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(54) Title: POLYNUCLEOTIDES, POLYPEPTIDES EXPRESSED BY THE POLYNUCLEOTIDES AND METHODS FOR THEIR USE

(57) Abstract: Novel polynucleotides including partial and extended sequences, and open reading frames, are provided, together with probes and primers, DNA constructs comprising the polynucleotides, biological materials and organisms incorporating the polynucleotides, polypeptides expressed by the polynucleotides, and methods for using the polynucleotides and polypeptides.

POLYNUCLEOTIDES, POLYPEPTIDES EXPRESSED BY THE POLYNUCLEOTIDES AND METHODS FOR THEIR USE

Technical Field of the Invention

This invention relates to polynucleotides believed to be novel, including partial, extended and full length sequences, as well as probes and primers, genetic constructs comprising the polynucleotides, biological materials incorporating the polynucleotides, polypeptides expressed by the polynucleotides, and methods for using the polynucleotides and polypeptides.

Background of the Invention

Sequencing of the genomes, or portions of the genomes, of numerous biological materials, including humans, animals, microorganisms and various plant varieties, has been and is being carried out on a large scale. Polynucleotides identified using sequencing techniques may be partial or full-length genes, and may contain open reading frames, or portions of open reading frames, that encode polypeptides. Putative polypeptides may be determined based on polynucleotide sequences. The sequencing data relating to polynucleotides thus represents valuable and useful information.

Polynucleotides may be analyzed for various degrees of novelty by comparing identified sequences to sequences published in various public domain databases, such as EMBL. Newly identified polynucleotides and putative polypeptides may also be compared to polynucleotides and polypeptides contained in public domain information to ascertain homology to known polynucleotides and polypeptides. In this way, the degree of similarity, identity or homology of polynucleotides and polypeptides of unknown function may be determined relative to polynucleotides and polypeptides having known functions.

Information relating to the sequences of isolated polynucleotides may be used in a variety of ways. Specified polynucleotides having a particular sequence may be isolated, or synthesized, for use in *in vivo* or *in vitro* experimentation as

probes or primers. Alternatively, collections of sequences of isolated polynucleotides may be stored using magnetic or optical storage medium, and analyzed or manipulated using computer hardware and software, as well as other types of tools.

Summary of the Invention

The present invention relates to polynucleotide sequences identified in the attached Sequence Listing as SEQ ID NOS: 1-35, variants of those sequences, extended sequences comprising the sequences set out in SEQ ID NOS: 1-35 and their variants, probes and primers corresponding to the sequences set out in SEQ ID NOS: 1-35 and their variants, polynucleotides comprising at least a specified number of contiguous residues of any of the polynucleotides identified as SEQ ID NOS: 1-35 (*x*-mers), and extended sequences comprising portions of the sequences set out in SEQ ID NOS: 1-35, all of which are referred to herein, collectively, as "polynucleotides of the present invention."

The polynucleotide sequences identified as SEQ ID NOS: 1-35 were derived from mammalian sources, namely, from mouse airways induced eosinophilia, rat dermal papilla and mouse stromal cells. Some of the polynucleotides of the present invention are "partial" sequences, in that they do not represent a full-length gene encoding a full-length polypeptide. Such partial sequences may be extended by further analyzing and sequencing the EST clones from which the sequences were obtained, or by analyzing and sequencing various DNA libraries (e.g. cDNA or genomic) using primers and/or probes and well known hybridization and/or PCR techniques. The partial sequences identified as SEQ ID NOS: 1-35 may thus be extended until an open reading frame encoding a polypeptide, a full-length polynucleotide and/or gene capable of expressing a polypeptide, or another useful portion of the genome is identified. Such extended sequences, including full-length polynucleotides and genes, are described as "corresponding to" a sequence identified as one of the sequences of SEQ ID NOS: 1-35 or a variant thereof, or a portion of one of the sequences of SEQ ID NOS: 1-35 or a variant thereof, when the extended polynucleotide comprises an identified

sequence or its variant, or an identified contiguous portion (x-mer) of one of the sequences of SEQ ID NOS: 1-35 or a variant thereof.

The polynucleotides identified as SEQ ID NOS: 1-35 were isolated from mouse and rat cDNA clones and represent sequences that are expressed in the tissue from which the cDNA was prepared. The sequence information may be used to isolate or synthesize expressible DNA molecules, such as open reading frames or full-length genes, that can then be used as expressible or otherwise functional DNA in transgenic mammals and other organisms. Similarly, RNA sequences, reverse sequences, complementary sequences, anti-sense sequences and the like, corresponding to the polynucleotides of the present invention, may be routinely ascertained and obtained using the cDNA sequences identified as SEQ ID NOS: 1-35.

In a first aspect, the present invention provides isolated polynucleotide sequences comprising a polynucleotide selected from the group consisting of: (a) sequences recited in SEQ ID NO: 1-35; (b) complements of the sequences recited in SEQ ID NO: 1-35; (c) reverse complements of the sequences recited in SEQ ID NO: 1-35; (d) reverse sequences of the sequences recited in SEQ ID NO: 1-35; (e) sequences having either 40%, 60%, 75% or 90% identical nucleotides, as defined herein, to a sequence of (a) – (d); probes and primers corresponding to the sequences set out in SEQ ID NO: 1-35; polynucleotides comprising at least a specified number of contiguous residues of any of the polynucleotides identified as SEQ ID NO: 1-35; and extended sequences comprising portions of the sequences set out in SEQ ID NO: 1-35; all of which are referred to herein as "polynucleotides of the present invention". The present invention also provides isolated polypeptide sequences identified in the attached Sequence Listing as SEQ ID NO: 36-65; polypeptide variants of those sequences; and polypeptides comprising the isolated polypeptide sequences and variants of those sequences.

In another aspect, the present invention provides genetic constructs comprising a polynucleotide of the present invention, either alone, or in combination with one or more additional polynucleotides of the present invention,

or in combination with one or more known polynucleotides, together with cells and target organisms comprising such constructs.

The polynucleotides identified as SEQ ID NOS: 1-35 may contain open reading frames ("ORFs") or partial open reading frames encoding polypeptides. Additionally, open reading frames encoding polypeptides may be identified in extended or full-length sequences corresponding to the sequences set out as SEQ ID NOS: 1-35. Open reading frames may be identified using techniques that are well known in the art. These techniques include, for example, analysis for the location of known start and stop codons, most likely reading frame identification based on codon frequencies, etc. Suitable tools and software for ORF analysis are available, for example, on the Internet at http://www.ncbi.nlm.nih.gov/gorf/gorf.html. Open reading frames and portions of open reading frames may be identified in the polynucleotides of the present invention. Once a partial open reading frame is identified, the polynucleotide may be extended in the area of the partial open reading frame using techniques that are well known in the art until the polynucleotide for the full open reading frame is identified. Thus, polynucleotides and open reading frames encoding polypeptides may be identified using the polynucleotides of the present invention.

Once open reading frames are identified in the polynucleotides of the present invention, the open reading frames may be isolated and/or synthesized. Expressible DNA constructs may then be constructed that comprise the open reading frames and suitable promoters, initiators, terminators, etc., which are well known in the art. Such DNA constructs may be introduced into a host cell to express the polypeptide encoded by the open reading frame. Suitable host cells may include various prokaryotic and eukaryotic cells.

Polypeptides encoded by the polynucleotides of the present invention may be expressed and used in various assays to determine their biological activity. Such polypeptides may be used to raise antibodies, to isolate corresponding interacting proteins or other compounds, and to quantitatively determine levels of interacting proteins or other compounds.

In another aspect, the present invention provides isolated polypeptides encoded, or partially encoded, by the above polynucleotides. As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full-length proteins, wherein the amino acid residues are linked by covalent peptide bonds. The term "polypeptide encoded by a polynucleotide" as used herein, includes polypeptides encoded by a polynucleotide that comprises an isolated polynucleotide sequence or variant provided herein. Polypeptides of the present invention may be naturally purified products, or may be produced partially or wholly using recombinant techniques. Such polypeptides may be glycosylated with bacterial, fungal, mammalian or other eukaryotic carbohydrates or may be non-glycosylated. In specific embodiments, the inventive polypeptides comprise an amino acid sequence selected from the group consisting of SEQ ID NO: 36-65.

Polypeptides of the present invention may be produced recombinantly by inserting a polynucleotide sequence that encodes the polypeptide into a genetic construct and expressing the polypeptide in an appropriate host. Any of a variety of genetic constructs known to those of ordinary skill in the art may be employed. Expression may be achieved in any appropriate host cell that has been transformed or transfected with a genetic construct containing a polynucleotide that encodes a recombinant polypeptide. Suitable host cells include prokaryotes, yeast, and higher eukaryotic cells. Preferably, the host cells employed are *Escherichia coli*, insect, yeast, or a mammalian cell line such as COS or CHO. The polynucleotide sequences expressed in this manner may encode naturally occurring polypeptides, portions of naturally occurring polypeptides, or other variants thereof.

In a related aspect, polypeptides are provided that comprise at least a functional portion of a polypeptide having an amino acid sequence encoded by a polynucleotide of the present invention. As used herein, the "functional portion" of a polypeptide is that portion which contains the active site essential for affecting the function of the polypeptide, for example, the portion of the molecule that is capable of binding one or more reactants. The active site may be made up

of separate portions present on one or more polypeptide chains and will generally exhibit high binding affinity.

Functional portions of a polypeptide may be identified by first preparing fragments of the polypeptide by either chemical or enzymatic digestion of the polypeptide, or by mutation analysis of the polynucleotide that encodes the polypeptide and subsequent expression of the resulting mutant polypeptides. The polypeptide fragments or mutant polypeptides are then tested to determine which portions retain biological activity, using, for example, the representative assays provided below.

Portions and other variants of the inventive polypeptides may also be generated by synthetic or recombinant means. Synthetic polypeptides having fewer than about 100 amino acids, and generally fewer than about 50 amino acids, may be generated using techniques well known to those of ordinary skill in the art. For example, such polypeptides may be synthesized using any of the commercially available solid-phase techniques, such as the Merrifield solid-phase synthesis method, where amino acids are sequentially added to a growing amino acid chain. *See* Merrifield, *J. Am. Chem. Soc.* 85:2149-2154, 1963. Equipment for automated synthesis of polypeptides is commercially available from suppliers such as Perkin Elmer/Applied BioSystems, Inc. (Foster City, California), and may be operated according to the manufacturer's instructions. Variants of a native polypeptide may be prepared using standard mutagenesis techniques, such as oligonucleotide-directed, site-specific mutagenesis (Kunkel, *Proc. Natl. Acad. Sci. USA* 82:488-492, 1985). Sections of polynucleotide sequence may also be removed using standard techniques to permit preparation of truncated polypeptides.

In general, the polypeptides disclosed herein are prepared in an isolated, substantially pure, form. Preferably, the polypeptides are at least about 80% pure, more preferably at least about 90% pure, and most preferably at least about 99% pure. In certain embodiments, described in detail below, the isolated polypeptides are incorporated into pharmaceutical compositions or vaccines.

The present invention also contemplates methods for modulating the polynucleotide and/or polypeptide content and composition of an organism, such methods involving stably incorporating into the genome of the organism a construct containing DNA of the present invention. In one embodiment, the target organism is a mammal, preferably a human, for example for human gene therapy. In a related aspect, a method for producing an organism having an altered genotype or phenotype is provided, the method comprising transforming a cell with a DNA construct of the present invention to provide a transgenic cell, and cultivating the transgenic cell under conditions conducive to regeneration and mature organism growth.

The isolated polynucleotides of the present invention have utility in genome mapping, in physical mapping, and in positional cloning of genes. Additionally, the polynucleotide sequences identified as SEQ ID NOS: 1-35 and their variants may be used to design oligonucleotide probes and primers. Oligonucleotide probes and primers have sequences that are substantially complementary to the polynucleotide of interest over a certain portion of the polynucleotide. Oligonucleotide probes designed using the polynucleotides of the present invention may be used to detect the presence and examine the expression patterns of genes in any organism having sufficiently similar DNA and RNA sequences in their cells using techniques that are well known in the art, such as slot blot DNA hybridization techniques. Oligonucleotide primers designed using the polynucleotides of the present invention may be used for PCR amplifications. Oligonucleotide probes and primers designed using the polynucleotides of the present invention may also be used in connection with various microarray technologies, including the microarray technology of Affymetrix (Santa Clara, CA).

The polynucleotides of the present invention may also be used to tag or identify an organism or reproductive material therefrom. Such tagging may be accomplished, for example, by stably introducing a non-disruptive non-functional heterologous polynucleotide identifier into an organism, the polynucleotide comprising one of the polynucleotides of the present invention.

Detailed Description

Polynucleotides were isolated by high throughput sequencing of cDNA libraries prepared from mouse airway-induced eosinophilia, rat dermal papilla and mouse stromal cells as described below, in Example 1. Isolated polynucleotides of the present invention include the polynucleotides identified as SEQ ID NOS: 1-35; isolated polynucleotides comprising a polynucleotide sequence selected from the group consisting of SEQ ID NOS: 1-35; isolated polynucleotides comprising at least a specified number of contiguous residues (*x*-mers) of any of the polynucleotides identified as SEQ ID NOS: 1-35; polynucleotides complementary to any of the above polynucleotides; anti-sense sequences corresponding to any of the above polynucleotides; and variants of any of the above polynucleotides, as that term is described in this specification. The present invention also provides isolated polypeptide sequences identified in the attached Sequence Listing as SEQ ID NO: 36-65; polypeptide variants of those sequences; and polypeptides comprising the isolated polypeptide sequences and variants of those sequences.

The correspondence of isolated polynucleotides encoding isolated polypeptides of the present invention, and the functionality of the polypeptides, are shown, below, in Table 1.

Table 1

SEQ ID NO Poly-nucleotides	SEQ ID NO Poly-peptides	Activity Category	Functionality
1	36	Secretory molecule	Hypothetical 131.1 kDa protein
2	37	Secretory molecule/cytokine/ cell signaling	ZCYTO7 belongs to a family of IL-17-related cytokines differing in patterns of expression and proinflammatory responses that may be transduced through a cognate set of cell surface receptors. IL-17 is a T cell-derived cytokine that may play an important role in the initiation or maintenance of the proinflammatory response. Whereas expression of IL-17 is restricted to activated T cells, the IL-17 receptor is found to be

			widely expressed, a finding consistent with the pleiotropic activities of IL-17.
3	38	Secretory molecule	Novel
4	39	Receptor/cytokine/ cell signaling	Tumor endothelial marker 1 precursor
5	40	Secretory molecule	ERO1-L (ERO1-like protein) is involved in oxidative endoplasmic reticulum (ER) protein folding in mammalian cells. Oxidizing conditions must be maintained in the ER to allow the formation of disulfide bonds in secretory proteins. A family of conserved genes, termed ERO for ER oxidoreductins, plays a key role in this process. ERO1-L is a type II integral membrane protein.
6	41	Secretory molecule	Novel
7	42	Receptor/transcriptio n factor	EMR2 is an EGF-like module that is part of the epidermal growth factor (EGF)-TM7 proteins, which also include EMR1, (EGF-like molecule containing mucin-like hormone receptor 1) F4/80, and CD97. These proteins constitute a recently defined class B GPCR subfamily and are predominantly expressed on leukocytes. These molecules possess N-terminal EGF-like domains coupled to a seven-span transmembrane (7TM) moiety via a mucin-like spacer domain. EMR2 contains a total of five tandem EGF-like domains and expresses similar protein isoforms consisting of various numbers of EGF-like domains as a result of alternative RNA splicing. EMR2 share many characteristics with CD97, including highly homologous EGF-like domains and identical gene organization, indicating that both genes are the products of a recent gene duplication event. Both EMR2 and CD97 are highly expressed in immune tissues; however, unlike

			CD97, which is ubiquitously expressed in most cell types, EMR2 expression is restricted to monocytes, macrophages
8	43	Secretory molecule/ cell structure/motility, extracellular matrix	Bone/cartilage proteoglycan I (BGN) is also known as biglycan or PG-S1. BGN is found in the extracellular matrices of several connective tissues, especially in articular cartilages. The two glycosaminoglycan chains attached to BGN can be either chondroitin sulfate or dermatan sulfate. BGN belongs to the small interstitial proteoglycans family. BGN is a small leucine-rich proteoglycan and is a nonfibrillar extracellular matrix component with functions that include the positive regulation of bone formation. It is synthesized as a precursor with an NH(2)-terminal propeptide that is cleaved to yield the mature form found in vertebrate tissues. Bone morphogenetic protein-1 (BMP-1) cleaves proBGN at a single site, removing the propeptide and producing BGN. Soluble BGN purified from rat thymic myoid cells had hemopoietic activity capable of inducing preferential growth and differentiation of monocytic lineage cells from various hemopoietic sources, including brain microglial cells. The haemopoietic BGN plays an important role in generating brain-specific circumstances for development of microglial/monocytic cells
9	44	Secretory molecule	Tubulointerstitial nephritis antigen (TIN-ag) is a basement membrane glycoprotein reactive with autoantibodies in some forms of immunologically mediated human tubulointerstitial nephritis. TIN1 and TIN2 are alternatively spliced products of the TIN-Ag gene. The

			open reading frames of TIN1 and TIN2 indicates the presence of a signal peptide and putative pre-propeptide and both forms contain putative calcium-binding sites. TIN1 additionally contains a characteristic laminin-like epidermal growth factor (EGF) motif and significant homology within the carboxy terminus with the cysteine proteinase family of enzymes. The EGF motif bears important similarities in the positions of cysteines with two motifs in the propeptide of von Willebrand factor. The EGF motif and part of the region that is homologous with the cysteine proteinase family are removed from the TIN2 cDNA. The rest of the TIN1 and TIN2 sequences are identical. TIN-ag is expressed mainly in the kidney and in the intestinal epithelium.
10		Receptor-like molecule	Novel
11	45	Secretory molecule/ gene/protein expression, RNA synthesis, transcription factors	Toso is a cell surface, specific regulator of Fas-induced apoptosis in T cells. Fas is a surface receptor that can transmit signals for apoptosis. Toso is expressed in lymphoid cells and expression is enhanced after cell-specific activation processes in T cells. Toso appeared limited to inhibition of apoptosis mediated by members of the TNF receptor family and was capable of inhibiting T cell self-killing induced by TCR activation processes that up-regulate Fas ligand. Toso inhibits caspase-8 processing, the most upstream caspase activity in Fas-mediated signaling, potentially through activation of cFLIP. Toso therefore serves as a novel regulator of Fas-mediated apoptosis and may act as a regulator of cell fate in T cells and

			other hematopoietic lineages.
12	46	Secretory molecule/ gene/protein expression, RNA synthesis, transcription factors	Surface glycoprotein CD59 is a phosphatidyl-inositol-glycan-anchored glycoprotein involved in T-cell activation and restriction of complement-mediated lysis. It is also known as protectin, and is ubiquitously expressed on benign and malignant cells. CD59 inhibits complement (C)-mediated lysis of target cells by preventing the formation of the membrane attack complex, in the terminal step of C-ctivation. Recent experimental evidence demonstrates that CD59 is the main restriction factor of C-mediated lysis of malignant cells of different histotypes. Additionally, a soluble form of CD59, that retains its anchoring ability and functional properties, has been identified in body fluids and in culture supernatants of different malignant cells. CD59 may protect neoplastic cells from C-mediated lysis, contributing to their escape from innate C-control and to tumor progression. The expression of CD59 by neoplastic cells may contribute to impair the therapeutic efficacy of C-activating monoclonal antibodies (mAb) directed to tumor-associated antigens. CD59 can be utilized to improve the therapeutic efficacy of clinical approaches of humoral immunotherapy with C-activating mAb in human malignancies.
13	47	Secretory molecules/cell or organism defense, homeostasis, detoxification	Cytochrome B561 (cyb561) is a secretory vesicle-specific electron transport protein unique to neuroendocrine secretory vesicles. It binds two heme groups non-covalently and is an integral membrane protein. It acts as an electron channel and mediates

			equilibration of ascorbate-semidehydroascorbate inside the secretory vesicle with the ascorbate redox pair in the cytoplasm. The role for this function is to regenerate ascorbate inside the secretory vesicle for use by monooxygenases. The secretory vesicles contain catecholamines and amidated peptides. Cyb561 belongs to the eukaryotic b561 family.
14	48	Secretory molecule	Novel
15	49	Receptor-like molecule/ gene or protein expression, RNA synthesis, transcription factor	High affinity immunoglobulin epsilon receptor beta-subunit (FCER1) is also known as IgE Fc receptor, beta-subunit, FCER1b or FCE1b. FCER1 binds to the Fc region of immunoglobulins epsilon and is a high affinity receptor. FCER1 plays a role in initiating the allergic response where binding of allergen to receptor-bound IgE leads to cell activation and the release of mediators, such as histamine. FCER1 is responsible for the manifestations of allergy and induces the secretion of important lymphokines. It functions as a tetramer consisting of an alpha chain, a beta chain, and two disulfide-linked gamma chains and is an integral membrane protein. Variants of the FCER1B gene have been identified, which are associated with an increased risk of developing atopy and bronchial asthma. Atopic dermatitis is a common skin disease frequently associated with allergic disorders such as allergic rhinitis and asthma.
16	50	Receptor-like molecule	Hypothetical 10.3 kDa protein
17	51	Secretory molecule/antigen processing	Lysosomal thiol reductase IP30 catalyzes disulfide bond reduction both *in vitro* and *in vivo* and is optimally active at acidic pH. IP30

			is important in disulfide bond reduction of proteins delivered to MHC class II-containing compartments and consequently in antigen processing. IP30 can be mediated by multiple lysosomal proteases. Proteins internalized into the endocytic pathway are usually degraded. Efficient proteolysis requires denaturation, induced by acidic conditions within lysosomes, and reduction of inter- and intrachain disulfide bonds. The active site, determined by mutagenesis, consists of a pair of cysteine residues separated by two amino acids, similar to other enzymes of the thioredoxin family.
18		Receptor-like molecule	RNA binding protein.
19	52	Secretory molecule/cellular	Notch4-like protein (ZNEU1) is part of the NOTCH4 family that encodes receptors responsible for cell fate decisions during development. These Notch receptors and their ligands, Delta and Jagged, have been implicated in several diseases. When truncated, constitutively active mutant forms of the Notch receptor appear to be involved in T-cell leukemia, mammary carcinomas and a tumorous germline phenotype. Notch4 genes are expressed specifically in endothelial cells.
20	53	Secretory molecule	Novel
21	54	Secretory molecule/transporter	Serotransferrin (siderophilin) (Tf) or beta-1-metal binding globulin is part of the transferrin family. Transferrins are iron binding transport proteins which can bind two atoms of ferric iron in association with the binding of an anion, usually bicarbonate. Tf is responsible for the transport of iron from sites of absorption and heme degradation to those of storage and

			utilization. Serum transferrin also has a further role in stimulating cell proliferation. Tf gene expression is modulated by vitamin A, testosterone, and peptide hormones.
22	55	Secretory molecule/ gene or protein expression, RNA synthesis, transcription factor	Insulin-like growth factor binding protein 5 protease (IGFBP-5) modulates the effects of insulin growth factors (IGFs) on cells. IGFBP-5 is synthesized by smooth muxcle cells and binds to the extracellular matrix. It is also secreted into conditioned medium of cultured cells and is cleaved into fragments by a concomitantly produced protease. These fragments have reduced affinity for the IGFs. IGFBP-5 protease belongs to a family of serine-metallo proteases.
23	56	Secretory molecule/cellular development	Major epididymis-specific protein E4 is also known as epididymal protein BE-20. It belongs to WAP-type 'four-disulfide core' family and plays a role in the maturation of spermatozoa during its movement through the epididymis and the capacity of sperm to fertilize ova. Expression of E4 was located to the epithelial cells of the cauda epididymis and proximal segment of the ductus deferens by in situ hybridization. No expression was found in sections of the corpus and caput epididymis, testis, and liver.
24		Secretory molecule/cell signaling	TNFR-related death receptor-6 DR6 contains an extracellular region containing varying numbers of cysteine-rich domains and an intracellular region that contains the death domain. Death receptors are activated in a ligand-dependent or independent manner and transduce apoptotic signals via their respective intracellular death domains.
25	57	Receptor-like molecule	Novel

26	58	Secretory molecule/regulation	Channel inducing factor precursor (CHIF) or corticosteroid-induced protein induces a potassium channel when expressed in *Xenopus* oocytes and activates endogenous oocyte transport proteins. It is a type I membrane protein selectively present in the distal parts of the nephron (medullary and papillary collecting ducts and end portions of cortical collecting tubule) and in the epithelial cells of the distal colon. No expression is found in renal proximal tubule, loop of Henle and distal tubule, proximal colon, small intestine, lung, choroid plexus, salivary glands, or brain. CHIF belongs to the ATP1G1 /PLM / Mat-8 family and exhibits significant homologies with proteins that are putatively regulatory (phospholemman, gamma-subunit of Na(+)-K(+)-ATPase, Mat-8).
27	59	Secretory molecule	Hepatocellular carcinoma-associated antigen 112.
28	60	Receptor-like molecule/homeostasis	Lymphatic endothelium-specific hyaluronan receptor LYVE-1 is a major receptor for hyaluronan (HA) on the lymph vessel wall molecule that binds both soluble and immobilized HA. LYVE-1 plays a role in the control of the HA pathway. The extracellular matrix glycosaminoglycan hyaluronan (HA) is an abundant component of skin and mesenchymal tissues where it facilitates cell migration during wound healing, inflammation, and embryonic morphogenesis. Both during normal tissue homeostasis and particularly after tissue injury, HA is mobilized from these sites through lymphatic vessels to the lymph nodes where it is degraded before entering the circulation for rapid uptake by the liver. LYVE-1 is similar to the

			CD44 HA receptor, but in contrast to CD44, LYVE-1 colocalizes with HA on the luminal face of the lymph vessel wall and is completely absent from blood vessels.
29	61	Receptor-like molecule/cell signaling	G protein-coupled receptor GPR35 is an integral membrane protein that belongs to family 1 of G-protein coupled receptors (GPRC). The GPCR family shares a structural motif of seven transmembrane segments with large numbers of conserved residues in those regions.
30	62	Receptor-like molecule	Tumor-associated glycoprotein E4 is also known as Taa1 or Tage4 and belongs to the immunoglobulin superfamily. This family contains cell adhesion molecules which have wide-ranging functions and mediate a variety of homotypic and heterotypic cellular interactions playing a general role in cell surface recognition. The Tage4 gene product is closely related to the hepatocellular carcinoma antigen TuAg.1. Tage4 is a glycoprotein expressed at the surface of colon carcinoma cell lines, but at a very low level in normal adult colon and lung tissue and not in normal tissues tested.
31	63	Secretory molecule	Hypothetical 28.6 kDa protein is also known as plunc, for palate, lung, and nasal epithelium clone. Expression of plunc is associated with the palate, nasal septum, and nasal conchae. It is also expressed strongly in the trachea and bronchi of the adult lung. No significant homologies with known genes were observed at the nucleotide level and limited amino acid homology with two salivary gland-specific proteins was noted. The amino acid sequence revealed consensus sequences for N-glycosylation, protein kinase C and

			casein kinase phosphorylation, as well as a leucine zipper. In addition, an unique amino acid sequence repeat sequence is located near the amino-terminal portion of the protein.
32	64	Secretory molecule	Claudin-18 (Cldn18) is a component of tight junction (TJ) strands and belongs to the claudin family. Claudins are integral membrane protein component of tight junctions, a structure controlling cell-to-cell adhesion and, consequently, regulating paracellular and transcellular transport of solutes across epithelia and endothelia. The claudin family also includes occludin and 17 other distinct claudins. Claudin family members are tetra-span transmembrane proteins that are localized in cell-specific TJs. In multicellular organisms, various compositionally distinct fluid compartments are established by epithelial and endothelial cellular sheets. For these cells to function as barriers, TJs are considered to create a primary barrier for the diffusion of solutes through the paracellular pathway. Claudins are therefore responsible for TJ-specific obliteration of the intercellular space.
33		Secretory molecule	Glutamine repeat protein 1 (GRP-1) contains simple tandem repeats of the trinucleotide sequence CAG that encode homopolymeric stretches of glutamine. Although polyglutamine has been identified in diverse proteins, it is present predominantly in transcription factors. Greater than two-thirds of GRP-1 are only two amino acids, namely glutamine (50%) and histidine (18%). There are four polyglutamine motifs interspersed with histidine-rich regions. There is also a putative

			nuclear localization signal flanked by sites for possible serine phosphorylation. GRP-1 mRNA was expressed constitutively in some macrophage cell lines and B and T cell lines. Interferon-gamma or lipopolysaccharide augmented GRP-1 mRNA expression in the mouse macrophage cell line ANA-1. Because polyglutamine motifs can cause protein oligomerization and can function as transcriptional activation domains, GRP-1 is a transcription factor associated with interferon-gamma- or lipopolysaccharide-induced activation of macrophages.
34		Secretory molecule	Alpha-1 collagen
35	65	Receptor-like molecule/Cell signaling	Gdnf family receptor alpha 4, transmembrane isoform (Gfra4) is a members of the Gdnf protein family that signal through receptors consisting of a GPI-linked GFRalpha subunit and the transmembrane tyrosine kinase Ret. Gfra4 is expressed in many tissues, including nervous system, in which intron retention leads to a putative intracellular or secreted GFRalpha4 protein. Efficient splicing occurs only in thyroid, parathyroid, and pituitary and less in adrenal glands. A splice form that leads to a GPI-linked GFRalpha4 receptor is expressed in juvenile thyroid and parathyroid glands. In newborn and mature thyroid as well as in parathyroid and pituitary glands major transcripts encode for a putative transmembrane isoform of GFRalpha4. GFRalpha4 expression may restrict the inherited cancer syndrome multiple endocrine neoplasia type 2, associated with mutations in RET, to these cells.

The word "polynucleotide(s)," as used herein, means a polymeric collection of nucleotides and includes DNA and corresponding RNA molecules and both single and double stranded molecules, including HnRNA and mRNA molecules, sense and anti-sense strands of DNA and RNA molecules, and comprehends cDNA, genomic DNA, and wholly or partially synthesized polynucleotides. An HnRNA molecule contains introns and "corresponds to" a DNA molecule in a generally one-to-one manner. An mRNA molecule "corresponds to" an HnRNA and DNA molecule from which the introns have been excised. A polynucleotide of the present invention may be an entire gene, or any portion thereof. A gene is a DNA sequence which codes for a functional protein or RNA molecule. Operable anti-sense polynucleotides may comprise a fragment of the corresponding polynucleotide, and the definition of "polynucleotide" therefore includes all operable anti-sense fragments. Anti-sense polynucleotides and techniques involving anti-sense polynucleotides are well known in the art and are described, for example, in Robinson-Benion *et al.*, *Methods in Enzymol.* 254(23): 363-375, 1995 and Kawasaki *et al.*, *Artific. Organs* 20 (8): 836-848, 1996.

Identification of genomic DNA and heterologous species DNA can be accomplished by standard DNA/DNA hybridization techniques, under appropriately stringent conditions, using all or part of a cDNA sequence as a probe to screen an appropriate library. Alternatively, PCR techniques using oligonucleotide primers that are designed based on known genomic DNA, cDNA and/or protein sequences can be used to amplify and identify genomic and cDNA sequences. Synthetic DNA corresponding to the identified sequences and variants may be produced by conventional synthesis methods. All of the polynucleotides described herein are isolated and purified, as those terms are commonly used in the art.

As used herein, the term "oligonucleotide" refers to a relatively short segment of a polynucleotide sequence, generally comprising between 6 and 60 nucleotides, and comprehends both probes for use in hybridization assays and primers for use in the amplification of DNA by polymerase chain reaction.

As used herein, the term "*x*-mer," with reference to a specific value of "*x*," refers to a polynucleotide comprising at least a specified number ("*x*") of contiguous residues of any of the polynucleotides identified as SEQ ID NOS: 1-35. The value of *x* may be from about 20 to about 600, depending upon the specific sequence.

As used herein, the term "polypeptide" encompasses amino acid chains of any length, including full-length proteins, wherein amino acid residues are linked by covalent peptide bonds. Polypeptides of the present invention may be naturally purified products, or may be produced partially or wholly using recombinant techniques. Such polypeptides may be glycosylated with mammalian or other eukaryotic carbohydrates or may be non-glycosylated.

According to one embodiment, "variants" of the polynucleotides of the present invention, including the polynucleotides set forth as SEQ ID NOS: 1-35, as that term is used herein, comprehends polynucleotides producing an "E" value of 0.01 or less, as described below, or having at least a specified percentage identity to a polynucleotide of the present invention, as described below. Polynucleotide variants of the present invention may be naturally occurring allelic variants, or non-naturally occurring variants.

Polynucleotide and polypeptide sequences may be aligned, and percentages of identical residues in a specified region may be determined against another polynucleotide or polypeptide, using computer algorithms that are publicly available. Two exemplary algorithms for aligning and identifying the similarity of polynucleotide sequences are the BLASTN and FASTA algorithms. Polynucleotides may also be analyzed using the BLASTX algorithm, which compares the six-frame conceptual translation products of a nucleotide query sequence (both strands) against a protein sequence database. The percentage identity of polypeptide sequences may be examined using the BLASTP algorithm. The BLASTN, BLASTP and BLASTX algorithms are available on the NCBI anonymous FTP server (ftp://ncbi.nlm.nih.gov) under /blast/executables/ and are available from the National Center for Biotechnology Information (NCBI), National Library of Medicine, Building 38A, Room 8N805, Bethesda, MD 20894,

USA. The BLASTN algorithm Version 2.0.11 [Jan-20-2000], set to the parameters described below, is preferred for use in the determination of polynucleotide variants according to the present invention. The BLASTP algorithm, set to the parameters described below, is preferred for use in the determination of polypeptide variants according to the present invention. The use of the BLAST family of algorithms, including BLASTN, BLASTP and BLASTX, is described at NCBI's website at URL http://www.ncbi.nlm.nih.gov/BLAST/newblast.html and in the publication of Altschul, *et al.*, *Nucleic Acids Res.* 25: 3389-3402, 1997.

The FASTA and FASTX algorithms are available on the Internet at the ftp site ftp://ftp.virginia.edu/pub/, and from the University of Virginia by contacting David Hudson, Vice Provost for Research, University of Virginia, P.O. Box 9025, Charlottesville, VA 22906-9025, USA. The FASTA algorithm, set to the default parameters described in the documentation and distributed with the algorithm, may be used in the determination of polynucleotide variants. The readme files for FASTA and FASTX Version 1.0x that are distributed with the algorithms describe the use of the algorithms and describe the default parameters. The use of the FASTA and FASTX algorithms is described in Pearson and Lipman, *Proc. Natl. Acad. Sci. USA* 85:2444-2448, 1988; and Pearson, *Methods in Enzymol.* 183:63-98, 1990. The following running parameters are preferred for determination of alignments and similarities using BLASTN that contribute to the E values and percentage identity: Unix running command with default parameter values thus: blastall -p blastn -d embldb -e 10 -G 0 -E 0 -r 1 -v 30 -b 30 -i queryseq –o results; the Parameters are : -p Program Name [String]; -d Database [String]; -e Expectation value (E) [Real]; -G Cost to open a gap (zero invokes default behavior) [Integer]; -E Cost to extend a gap (zero invokes default behavior) [Integer]; -r Reward for a nucleotide match (BLASTN only) [Integer]; -v Number of one-line descriptions (V) [Integer]; -b Number of alignments to show (B) [Integer]; -i Query File [File In]; -o BLAST report Output File [File Out] Optional.

The "hits" to one or more database sequences by a queried sequence produced by BLASTN or FASTA or a similar algorithm align and identify similar portions of sequences. The hits are arranged in order of the degree of similarity and the length of sequence overlap. Hits to a database sequence generally represent an overlap over only a fraction of the sequence length of the queried sequence.

The BLASTN and FASTA algorithms produce "Expect" values for alignments. The Expect value (E) indicates the number of hits one can "expect" to see over a certain number of contiguous sequences by chance when searching a database of a certain size. The Expect value is used as a significance threshold for determining whether the hit to a database, such as the preferred EMBL database, indicates true similarity. For example, an E value of 0.1 assigned to a hit is interpreted as meaning that in a database of the size of the EMBL database, one might expect to see 0.1 matches over the aligned portion of the sequence with a similar score simply by chance. The aligned and matched portions of the sequences, then, have a probability of 90% of being the same by this criterion. For sequences having an E value of 0.01 or less over aligned and matched portions, the probability of finding a match by chance in the EMBL database is 1% or less using the BLASTN or FASTA algorithm.

According to one embodiment, "variant" polynucleotides, with reference to each of the polynucleotides of the present invention, preferably comprise sequences having the same number or fewer nucleic acids than each of the polynucleotides of the present invention and producing an E value of 0.01 or less when compared to the polynucleotide of the present invention. That is, a variant polynucleotide is any sequence that has at least a 99% probability of being the same as the polynucleotide of the present invention, measured as having an E value of 0.01 or less using the BLASTN or FASTA algorithms set at the default parameters. According to a preferred embodiment, a variant polynucleotide is a sequence having the same number or fewer nucleic acids than a polynucleotide of the present invention that has at least a 99% probability of being the same as the

polynucleotide of the present invention, measured as having an E value of 0.01 or less using the BLASTN or FASTA algorithms set at the default parameters.

Alternatively, variant polynucleotides of the present invention may comprise a sequence exhibiting at least about 40%, more preferably at least about 60%, more preferably yet at least about 75%, and most preferably at least about 90% similarity to a polynucleotide of the present invention, determined as described below. The percentage similarity is determined by aligning sequences using one of the BLASTN or FASTA algorithms, set at default parameters, and identifying the number of identical nucleic acids over the best aligned portion; dividing the number of identical nucleic acids by the total number of nucleic acids of the polynucleotide of the present invention; and then multiplying by 100 to determine the percentage similarity. For example, a polynucleotide of the present invention having 220 nucleic acids has a hit to a polynucleotide sequence in the EMBL database having 520 nucleic acids over a stretch of 23 nucleotides in the alignment produced by the BLASTN algorithm using the default parameters. The 23 nucleotide hit includes 21 identical nucleotides, one gap and one different nucleotide. The percentage similarity of the polynucleotide of the present invention to the hit in the EMBL library is thus 21/220 times 100, or 9.5%. The polynucleotide sequence in the EMBL database is thus not a variant of a polynucleotide of the present invention.

Alternatively, variant polynucleotides of the present invention hybridize to a polynucleotide of the present invention under stringent hybridization conditions. As used herein, "stringent conditions" mean prewashing in a solution of 6X SSC, 0.2% SDS; hybridizing at 65°C, 6X SSC, 0.2% SDS overnight; followed by two washes of 30 minutes each in 1X SSC, 0.1% SDS at 65°C and two washes of 30 minutes each in 0.2X SSC, 0.1% SDS at 65°C.

The present invention also encompasses allelic variants of the disclosed sequences, together with DNA sequences that differ from the disclosed sequences but which, due to the degeneracy of the genetic code, encode a polypeptide which is the same as that encoded by a DNA sequence disclosed herein. Thus, polynucleotides comprising sequences that differ from the polynucleotide

sequences recited in SEQ ID NOS: 1-35, or complements, reverse sequences, or reverse complements of those sequences as a result of conservative substitutions are contemplated by and encompassed within the present invention. Additionally, polynucleotides comprising sequences that differ from the polynucleotide sequences recited in SEQ ID NOS: 1-35, or complements, reverse complements, or reverse sequences as a result of deletions and/or insertions totaling less than 10% of the total sequence length are also contemplated by and encompassed within the present invention.

The polynucleotides of the present invention may be isolated from various DNA libraries, or may be synthesized using techniques that are well known in the art. The polynucleotides may be synthesized, for example, using automated oligonucleotide synthesizers (e.g. Beckman Oligo 1000M DNA Synthesizer) to obtain polynucleotide segments of up to 50 or more nucleic acids. A plurality of such polynucleotide segments may then be ligated using standard DNA manipulation techniques that are well known in the art of molecular biology. One conventional and exemplary polynucleotide synthesis technique involves synthesis of a single stranded polynucleotide segment having, for example, 80 nucleic acids, and hybridizing that segment to a synthesized complementary 85 nucleic acid segment to produce a 5-nucleotide overhang. The next segment may then be synthesized in a similar fashion, with a 5-nucleotide overhang on the opposite strand. The "sticky" ends ensure proper ligation when the two portions are hybridized. In this way, a complete polynucleotide of the present invention may be synthesized entirely *in vitro*.

SEQ ID NOS: 2, 3, 5, 7-9, 11, 12, 14, 15, 17, 19-21, 23, 26, 28 and 30-32 are full-length sequences. The remaining polynucleotides are referred to as "partial" sequences, in that they may not represent the full coding portion of a gene encoding a naturally occurring polypeptide. The partial polynucleotide sequences disclosed herein may be employed to obtain the corresponding full-length genes for various species and organisms by, for example, screening DNA expression libraries using hybridization probes based on the polynucleotides of the present invention, or using PCR amplification with primers based upon the

polynucleotides of the present invention. In this way one can, using methods well known in the art, extend a polynucleotide of the present invention upstream and downstream of the corresponding mRNA, as well as identify the corresponding genomic DNA, including the promoter and enhancer regions, of the complete gene. The present invention thus comprehends isolated polynucleotides comprising a sequence identified in SEQ ID NOS: 1-35, or a variant of one of the specified sequences, that encode a functional polypeptide, including full-length genes. Such extended polynucleotides may have a length of from about 50 to about 4,000 nucleic acids or base pairs, and preferably have a length of less than about 4,000 nucleic acids or base pairs, more preferably yet a length of less than about 3,000 nucleic acids or base pairs, more preferably yet a length of less than about 2,000 nucleic acids or base pairs. Under some circumstances, extended polynucleotides of the present invention may have a length of less than about 1,800 nucleic acids or base pairs, preferably less than about 1,600 nucleic acids or base pairs, more preferably less than about 1,400 nucleic acids or base pairs, more preferably yet less than about 1,200 nucleic acids or base pairs, and most preferably less than about 1,000 nucleic acids or base pairs.

Polynucleotides of the present invention comprehend polynucleotides comprising at least a specified number of contiguous residues (x-mers) of any of the polynucleotides identified as SEQ ID NOS: 1-35 or their variants. According to preferred embodiments, the value of x is preferably at least 20, more preferably at least 40, more preferably yet at least 60, and most preferably at least 80. Thus, polynucleotides of the present invention include polynucleotides comprising a 20-mer, a 40-mer, a 60-mer, an 80-mer, a 100-mer, a 120-mer, a 150-mer, a 180-mer, a 220-mer a 250-mer, or a 300-mer, 400-mer, 500-mer or 600-mer of a polynucleotide identified as SEQ ID NOS: 1-35 or a variant of one of the polynucleotides identified as SEQ ID NOS: 1-35.

Polynucleotide probes and primers complementary to and/or corresponding to SEQ ID NOS: 1-35, and variants of those sequences, are also comprehended by the present invention. Such oligonucleotide probes and primers are substantially complementary to the polynucleotide of interest. An

oligonucleotide probe or primer is described as "corresponding to" a polynucleotide of the present invention, including one of the sequences set out as SEQ ID NOS: 1-35 or a variant, if the oligonucleotide probe or primer, or its complement, is contained within one of the sequences set out as SEQ ID NOS: 1-35 or a variant of one of the specified sequences.

Two single stranded sequences are said to be substantially complementary when the nucleotides of one strand, optimally aligned and compared using, for example, the BLAST algorithm as described above, with the appropriate nucleotide insertions and/or deletions, pair with at least 80%, preferably at least 90% to 95%, and more preferably at least 98% to 100%, of the nucleotides of the other strand. Alternatively, substantial complementarity exists when a first DNA strand will selectively hybridize to a second DNA strand under stringent hybridization conditions. Stringent hybridization conditions for determining complementarity include salt conditions of less than about 1 M, more usually less than about 500 mM and preferably less than about 200 mM. Hybridization temperatures can be as low as 5°C, but are generally greater than about 22°C, more preferably greater than about 30°C and most preferably greater than about 37°C. Longer DNA fragments may require higher hybridization temperatures for specific hybridization. Since the stringency of hybridization may be affected by other factors such as probe composition, presence of organic solvents and extent of base mismatching, the combination of parameters is more important than the absolute measure of any one alone. The DNA from plants or samples or products containing plant material can be either genomic DNA or DNA derived by preparing cDNA from the RNA present in the sample.

In addition to DNA-DNA hybridization, DNA-RNA or RNA-RNA hybridization assays are also possible. In the case of DNA-RNA hybridization, the mRNA from expressed genes would then be detected instead of genomic DNA or cDNA derived from mRNA of the sample. In the case of RNA-RNA hybridization, RNA probes could be used. In addition, artificial analogs of DNA hybridizing specifically to target sequences could also be employed.

In specific embodiments, the oligonucleotide probes and/or primers comprise at least about 6 contiguous residues, more preferably at least about 10 contiguous residues, and most preferably at least about 20 contiguous residues complementary to a polynucleotide sequence of the present invention. Probes and primers of the present invention may be from about 8 to 100 base pairs in length or, preferably from about 10 to 50 base pairs in length or, more preferably from about 15 to 40 base pairs in length. The probes can be easily selected using procedures well known in the art, taking into account DNA-DNA hybridization stringencies, annealing and melting temperatures, potential for formation of loops and other factors, which are well known in the art. Tools and software suitable for designing probes, and especially suitable for designing PCR primers, are available on the Internet, for example, URL http://www.horizonpress.com/pcr/. Preferred techniques for designing PCR primers are also disclosed in Dieffenbach and Dyksler, *PCR primer: a laboratory manual.* Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1995.

A plurality of oligonucleotide probes or primers corresponding to a polynucleotide of the present invention may be provided in a kit form. Such kits generally comprise multiple DNA or oligonucleotide probes, each probe being specific for a polynucleotide sequence. Kits of the present invention may comprise one or more probes or primers corresponding to a polynucleotide of the present invention, including a polynucleotide sequence identified in SEQ ID NOS: 1-35.

In one embodiment useful for high-throughput assays, the oligonucleotide probe kits of the present invention comprise multiple probes in an array format, wherein each probe is immobilized in a predefined, spatially addressable location on the surface of a solid substrate. Array formats which may be usefully employed in the present invention are disclosed, for example, in U.S. Patents No. 5,412,087, 5,545,531, and PCT Publication No. WO 95/00530, the disclosures of which are hereby incorporated by reference.

Oligonucleotide probes for use in the present invention may be constructed synthetically prior to immobilization on an array, using techniques well known in

the art (see, for example, *Oligonucleotide Synthesis: A Practical Approach*, Gait, ed., IRL Press, Oxford, 1984). Automated equipment for the synthesis of oligonucleotides is available commercially from such companies as Perkin Elmer/Applied Biosystems Division (Foster City, CA) and may be operated according to the manufacturer's instructions. Alternatively, the probes may be constructed directly on the surface of the array using techniques taught, for example, in PCT Publication No. WO 95/00530.

The solid substrate and the surface thereof preferably form a rigid support and are generally formed from the same material. Examples of materials from which the solid substrate may be constructed include polymers, plastics, resins, membranes, polysaccharides, silica or silica-based materials, carbon, metals and inorganic glasses. Synthetically prepared probes may be immobilized on the surface of the solid substrate using techniques well known in the art, such as those disclosed in U.S. Patent No. 5,412,087.

In one such technique, compounds having protected functional groups, such as thiols protected with photochemically removable protecting groups, are attached to the surface of the substrate. Selected regions of the surface are then irradiated with a light source, preferably a laser, to provide reactive thiol groups. This irradiation step is generally performed using a mask having apertures at predefined locations using photolithographic techniques well known in the art of semiconductors. The reactive thiol groups are then incubated with the oligonucleotide probe to be immobilized. The precise conditions for incubation, such as temperature, time and pH, depend on the specific probe and can be easily determined by one of skill in the art. The surface of the substrate is washed free of unbound probe and the irradiation step is repeated using a second mask having a different pattern of apertures. The surface is subsequently incubated with a second, different, probe. Each oligonucleotide probe is typically immobilized in a discrete area of less than about 1 mm^2. Preferably each discrete area is less than about 10,000 mm^2, more preferably less than about 100 mm^2. In this manner, a multitude of oligonucleotide probes may be immobilized at predefined locations on the array.

The resulting array may be employed to screen for differences in organisms or samples or products containing genetic material as follows. Genomic or cDNA libraries are prepared using techniques well known in the art. The resulting target DNA is then labeled with a suitable marker, such as a radiolabel, chromophore, fluorophore or chemiluminescent agent, using protocols well known for those skilled in the art. A solution of the labeled target DNA is contacted with the surface of the array and incubated for a suitable period of time.

The surface of the array is then washed free of unbound target DNA and the probes to which the target DNA hybridized are determined by identifying those regions of the array to which the markers are attached. When the marker is a radiolabel, such as ^{32}P, autoradiography is employed as the detection method. In one embodiment, the marker is a fluorophore, such as fluorescein, and the location of bound target DNA is determined by means of fluorescence spectroscopy. Automated equipment for use in fluorescence scanning of oligonucleotide probe arrays is available from Affymetrix, Inc. (Santa Clara, CA) and may be operated according to the manufacturer's instructions. Such equipment may be employed to determine the intensity of fluorescence at each predefined location on the array, thereby providing a measure of the amount of target DNA bound at each location. Such an assay would be able to indicate not only the absence and presence of the marker probe in the target, but also the quantitative amount as well.

In this manner, oligonucleotide probe kits of the present invention may be employed to examine the presence/absence (or relative amounts in case of mixtures) of polynucleotides in different samples or products containing different materials rapidly and in a cost-effective manner.

Another aspect of the present invention involves collections of a plurality of polynucleotides of the present invention. A collection of a plurality of the polynucleotides of the present invention, particularly the polynucleotides identified as SEQ ID NOS: 1-35, may be recorded and/or stored on a storage medium and subsequently accessed for purposes of analysis, comparison, etc. One utility for such sets of sequences is the analysis of the set, either alone or together with other sequences sets, for single nucleotide polymorphisms (SNPs)

between sequences from different tissues and/or individuals for genetic studies, mapping and fingerprinting purposes. Suitable storage media include magnetic media such as magnetic diskettes, magnetic tapes, CD-ROM storage media, optical storage media, and the like. Suitable storage media and methods for recording and storing information, as well as accessing information such as polynucleotide sequences recorded on such media, are well known in the art. The polynucleotide information stored on the storage medium is preferably computer-readable and may be used for analysis and comparison of the polynucleotide information.

Another aspect of the present invention thus involves storage medium on which are recorded a collection of the polynucleotides of the present invention, particularly a collection of the polynucleotides identified as SEQ ID NOS: 1-35. According to one embodiment, the storage medium includes a collection of at least 20, preferably at least 50, more preferably at least 100, and most preferably at least 200 of the polynucleotides of the present invention, preferably the polynucleotides identified as SEQ ID NOS: 1-35, or variants of those polynucleotides.

Another aspect of the present invention involves a combination of polynucleotides, the combination containing at least 5, preferably at least 10, more preferably at least 20, and most preferably at least 50 different polynucleotides of the present invention, including polynucleotides selected from SEQ ID NOS: 1-35, or variants of these polynucleotides.

In another aspect, the present invention provides DNA constructs comprising, in the 5'-3' direction, a gene promoter sequence; an open reading frame coding for at least a functional portion of a polypeptide encoded by a polynucleotide of the present invention; and a gene termination sequence. The open reading frame may be orientated in either a sense or antisense direction. DNA constructs comprising a non-coding region of a gene coding for an enzyme encoded by the above DNA sequences or a nucleotide sequence complementary to a non-coding region, together with a gene promoter sequence and a gene termination sequence, are also provided. Preferably, the gene promoter and

termination sequences are functional in a host cell. More preferably, the gene promoter and termination sequences are common to those of the polynucleotide being introduced. Other promoter and termination sequences generally used in the art, such as the Cauliflower Mosaic Virus (CMV) promoter, with or without enhancers, such as the Kozak sequence or Omega enhancer, and *Agrobacterium tumefaciens* nopalin synthase terminator may be usefully employed in the present invention. Tissue-specific promoters may be employed in order to target expression to one or more desired tissues. The DNA construct may further include a marker for the identification of transformed cells.

Techniques for operatively linking the components of the DNA constructs are well known in the art and include the use of synthetic linkers containing one or more restriction endonuclease sites as described, for example, by Sambrook *et al.*, *Molecular Cloning: a laboratory manual*, Cold Spring Harbor Laboratory Press, Cold Spring Harbor, NY, 1989. The DNA constructs of the present invention may be linked to a vector having at least one replication system, for example, *Escherichia coli*, whereby after each manipulation, the resulting construct can be cloned and sequenced and the correctness of the manipulation determined.

Transgenic cells comprising the DNA constructs of the present invention are provided, together with organisms comprising such transgenic cells. Techniques for stably incorporating DNA constructs into the genome of target organisms, such as mammals, are well known in the art and include electroporation, protoplast fusion, injection into reproductive organs, injection into immature embryos, high velocity projectile introduction and the like. The choice of technique will depend upon the target organism to be transformed. In one embodiment, naked DNA is injected or delivered orally. Once the cells are transformed, cells having the DNA construct incorporated in their genome are selected. Transgenic cells may then be cultured in an appropriate medium, using techniques well known in the art.

In yet a further aspect, the present invention provides methods for modifying the level (concentration) or activity of a polypeptide in a host organism, comprising stably incorporating into the genome of the organism a

DNA construct of the present invention. The DNA constructs of the present invention may be used to transform a variety of organisms, including mammals, for example to make experimental gene knock out or transgenic animals.

Further, the polynucleotides of the present invention have particular application for use as non-disruptive tags for marking organisms, including commercially valuable animals, fish, bacteria and yeasts. DNA constructs comprising polynucleotides of the present invention may be stably introduced into an organism as heterologous, non-functional, non-disruptive tags. It is then possible to identify the origin or source of the organism at a later date by determining the presence or absence of the tag(s) in a sample of material.

Detection of the tag(s) may be accomplished using a variety of conventional techniques, and will generally involve the use of nucleic acid probes. Sensitivity in assaying the presence of probe can be usefully increased by using branched oligonucleotides, as described by Horn *et al.*, *Nucleic Acids Res.* 25(23):4842-4849, 1997, enabling to detect as few as 50 DNA molecules in the sample.

In particular, the polynucleotides of the present invention encode polypeptides that have important roles in processes such as induction of growth, differentiation of tissue-specific cells, cell migration, cell proliferation, and cell-cell interaction. These polypeptides are important in the maintenance of tissue integrity, and thus are important in processes such as wound healing. Some of these polypeptides act as modulators of immune responses, such as immunologically active polypeptides for the benefit of offspring. In addition, many polypeptides are immunologically active, making them important therapeutic targets in a whole range of disease states. Antibodies to the polypeptides of the present invention and small molecule inhibitors related to the polypeptides of the present invention may also be used for modulating immune responses and for treatment of diseases according to the present invention.

SEQ ID NOS: 1; 2; 4; 5; 6; 8; 9; 11; 12; 14; 17; 19-24; 26; 27; 31-34 encode secreted polypeptides. SEQ ID NOS: 10; 15; 16; 18; 25; 28; 30; and 35 encode polypeptides acting as receptors. SEQ ID NOS: 2; 4; 24; 29 and 35

encode polypeptides with cell signaling activity, which may be either intracellular or extracellular. Kinase genes, for example, encode polypeptides that phosphorylate specific substrates during cell-to-cell signaling. While some kinases are involved in normal metabolism and nucleotide production, others are significant for altering the activity of many cellular processes through the phosphorylation of specific proteins. Polypeptides encoded by these genes are important in the transmission of intracellular signals resulting from the binding of extracellular ligands such as hormones, growth factors or cytokines to membrane-bound receptors. The utility of polynucleotides encoding kinases resides in the manipulation of their signaling activities and downstream effects for the diagnosis and treatment of mammalian diseases that may be a consequence of inappropriate expression of these kinase genes.

SEQ ID NOS: 2 and 4 encode polypeptides with cytokine activity. Cytokine or growth factor polynucleotides encode polypeptides involved in intercellular signaling and represent another important class of molecules. Polynucleotides encoding such genes have utility in the diagnosis and treatment of disease.

SEQ ID NOS: 7; 11; 12; 15 and 22 encode polypeptides with transcription factor activity. These polynucleotides encode polypeptides required for the control of synthesis of proteins in tissue specific manner and have utility for the modification of protein synthesis for the control of disease.

SEQ ID NOS: 8 encode polypeptides acting in the extracellular matrix.

SEQ ID NOS: 11; 12; 15 and 22 encode polypeptides with RNA synthesis activities.

SEQ ID NO: 12 encodes a polypeptide having CD antigen activity. Such polynucleotides have utility as modulators of the composition, expression level and class of CD antigen expressed, which influence immune responses to self-antigens, neo-antigens and infectious agents.

Further exemplary specific utilities, for exemplary polynucleotides of the present invention, are specified in the Table below.

SEQ ID NO:	UTILITY
2	Promoting immune response as part of a vaccine or anti-cancer treatment. Inhibitors of this molecule can be useful as anti-inflammatory treatment, e.g. for autoimmune diseases or allergies.
11; 19	Utility as a target for cancer treatment and as an immunoregulatory and anti-inflammatory molecule
12	Diagnostic for specific types of cancer and for development of an anti-cancer treatment.
15	As a target for antagonists in the treatment of diseases such as asthma and allergy.
22	Useful to inhibit or enhance the activity of the soluble molecule that binds this protein.
28	Useful to promote or block cell trafficking and therefore in the treatment as anti-inflammatory and/or vaccine adjuvant where it can promoter inflammation.
35	Useful for tissue and neural regeneration.

The following examples are offered by way of illustration and not by way of limitation.

Example 1

ISOLATION OF CDNA SEQUENCES FROM MAMMALIAN EXPRESSION LIBRARIES

The cDNA sequences of the present invention were obtained by high-throughput sequencing of cDNA expression libraries constructed mouse airways-induced eosinophilia, rat dermal papilla and mouse stromal cells. The cDNA libraries were prepared as follows.

cDNA Library from Dermal Papilla (DEPA)

Dermal papilla cells from rat hair vibrissae (whiskers) were grown in culture and the total RNA extracted from these cells using established protocols. Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, MD), was used to obtain mRNA using a Poly(A) Quik mRNA isolation kit (Stratagene, La Jolla, CA), according to the manufacturer's

specifications. A cDNA expression library was then prepared from the mRNA by reverse transcriptase synthesis using a Lambda ZAP cDNA library synthesis kit (Stratagene).

cDNA library from mouse airway-induced eosinophilia (MALA)

Airway eosinophilia were induced in BALB/cByJ mice by administering 2 μg ovalbumin in 2 mg alum adjuvant intraperitoneally on day 0 and day 14, and subsequently 100 μg ovalbumin in 50 μl phosphate buffered saline (PBS) intranasally route on day 28. The accumulated eosinophils in the lungs were detected by washing the airways of the anesthetized mice with saline, collecting the washings (broncheolar lavage or BAL), and counting the numbers of eosinophils. The mice were sacrificed and total RNA was isolated from whole lung tissue using TRIzol Reagent (BRL Life Technologies). mRNA was isolated by using a Poly(A) Quik mRNA isolation kit (Stratagene, La Jolla, CA), according to the manufacturer's specifications. A cDNA expression library was then prepared from the mRNA by reverse transcriptase synthesis using a Lambda ZAP cDNA library synthesis kit (Stratagene).

cDNA Expression Library from Peripheral Lymph Node Stromal Cells (MLSA)

The peripheral axillary and brachial lymph nodes of BALB/cByJ mice with the flaky skin (*fsn*) mutation (Jackson Laboratories, Bar Harbour, MN) were dissected out. Single cell suspensions were obtained from the lymph nodes and cultured in tissue culture flasks at 10^7 cells /ml in 20% fetal calf serum and Dulbecco's Minimum Essential Medium. After 2 days the non-adherent cells were removed. The adherent cells were cultured for a further 2 days and then treated with 0.25 g/100ml Trypsin (ICN, Aurora, OH) and re-cultured. After a further 4 days, non-adherent cells were discarded and adherent cells removed by trypsinization. Remaining adherent cells were physically removed by scraping with a rubber policeman. All adherent stromal cells were pooled.

cDNA Expression Library from Flaky skin lymph node stromal cells in pBK-CMV (MLSA)

Stromal cells from Flaky skin mice lymph nodes were grown in culture and the total RNA extracted from these cells using established protocols. Total RNA, isolated using TRIzol Reagent (BRL Life Technologies, Gaithersburg, MD), was used to obtain mRNA using a Poly(A) Quik mRNA isolation kit (Stratagene, La Jolla, CA), according to the manufacturer's specifications. A cDNA expression library was then prepared from the mRNA by reverse transcriptase synthesis using a Lambda ZAP cDNA library synthesis kit (Stratagene).

cDNA sequences were obtained by high-throughput sequencing of the cDNA libraries described above using a Prism 377 sequencer (Perkin Elmer/Applied Biosystems Division, Foster City CA), and are provided in SEQ ID NO: 1-35, with corresponding polypeptide sequences in SEQ ID NOS: 36-65.

EXAMPLE 2

Analysis of cDNA sequences using BLAST algorithms

BLASTN Polynucleotide analysis

The isolated cDNA sequences were compared to sequences in the EMBL DNA database using the computer algorithm BLASTN. Comparisons of DNA sequences provided in SEQ ID NOS: 1-35, to sequences in the EMBL DNA database (using BLASTN) were made as of November, 2000, using Version 2.0.11 [Jan-20-2000], and the following Unix running command: blastall –p blastn –d embldb –e 10 –G0 –E0 –r 1 –v 30 –b 30 –i queryseq –o.

The sequences of SEQ ID NOS: 1, 3, 4, 6-11, 13, 18, 21, 22, 24, 25, 28-30, 33 and 34 were determined to have less than 50% identity, determined as described above, to sequences in the EMBL database using the computer algorithm BLASTN, as described above. The sequences of SEQ ID NOS: 2, 12, 14-16, 20 and 35 were determined to have less than 75% identity, determined as described above, to sequences in the EMBL database using the computer

algorithm BLASTN, as described above. The sequences of SEQ ID NOS: 17, 19, 23 and 27 were determined to have less than 90% identity, determined as described above, to sequences in the EMBL database using the computer algorithm BLASTN, as described above. Finally, the sequences of SEQ ID NOS: 5, 26 and 32 were determined to have less than 98% identity, determined as described above, to sequences in the EMBL database using the computer algorithm BLASTN, as described above.

BLASTP Polypeptide analysis

The sequences of SEQ ID NOS: 37, 41, 42, 44, 46-50, 55, 56 and 59 were determined to have less than 50% identity, determined as described above, to sequences in the SwissProt database using the computer algorithm BLASTP, as described above. The sequences of SEQ ID NOS: 36, 38, 43, 45 and 60 were determined to have less than 75% identity, determined as described above, to sequences in the SwissProt database using the computer algorithm BLASTP, as described above. The sequences of SEQ ID NOS: 39, 54 and 58 were determined to have less than 90% identity, determined as described above, to sequences in the SwissProt database using the computer algorithm BLASTP, as described above. Finally, the sequences of SEQ ID NOS: 53, 57, 62 and 65 were determined to have less than 98% identity, determined as described above, to sequences in the SwissProt database using the computer algorithm BLASTP, as described above.

BLASTX Polynucleotide Analysis

The sequences of SEQ ID NOS: 2-4, 6-16, 18, 22-24, 26-30 and 33-35 were determined to have less than 50% identity, determined as described above, to sequences in the SwissProt database using the computer algorithm BLASTX, as described above. The sequences of SEQ ID NOS: 1, 19, 20, 25 and 32 were determined to have less than 75% identity, determined as described above, to sequences in the SwissProt database using the computer algorithm BLASTX, as described above. Finally, the sequences of SEQ ID NOS: 5, 17, 21 and 31 were determined to have less than 90% identity, determined as described above, to

sequences in the SwissProt database using the computer algorithm BLASTX, as described above.

Example 2

ISOLATION AND CHARACTERIZATION OF THE HUMAN HOMOLOG OF MUKS1

This example demonstrates that an isolated cDNA may be used to isolate its homologue from a different species, the corresponding polypeptide may be expressed and the function of the polypeptide can be determined, starting the whole process from an isolated cDNA obtained as described above.

Analysis of RNA transcripts by Northern Blotting

Northern analysis to determine the size and distribution of mRNA for the clone muKS1 (SEQ ID NO: 66; isolated from a mouse keratinocyte stem cell cDNA library using high-throughput sequencing as described above) was performed by probing murine tissue mRNA blots with a probe consisting of nucleotides 268-499 of muKS1, radioactively labeled with [α^{32}P]-dCTP. Prehybridization, hybridization, washing and probe labeling were performed as described in Sambrook *et al.*, *Ibid.* mRNA for muKS1 was 1.6 kb in size and was observed to be most abundant in brain, lung, muscle and heart. Expression could also be detected in lower intestine, skin and kidney. No detectable signal was found in testis, spleen, liver, thymus and stomach.

Human homologue of muKS1

MuKS1 (SEQ ID NO: 66) was used to search the EMBL database (Release 50 plus updates to June, 1998) to identify human EST homologues. The top three homologies were to the following ESTs: accession numbers AA643952, HS1301003 and AA865643. These showed 92.63% identity over 285 nucleotides, 93.64% over 283 nucleotides and 94.035% over 285 nucleotides, respectively. Frame shifts were identified in AA643952 and HS1301003 when

translated. Combination of all three ESTs identified the human homologue huKS1 (SEQ ID NO: 67) and translated polypeptide SEQ ID NO: 67. Alignment of muKS1 and huKS1 polypeptides indicated 95% identity over 96 amino acids.

Bacterial expression and purification of muKS1 and huKS1

Polynucleotides 269-502 of muKS1 (SEQ ID NO: 69), encoding amino acids 23-99 of polypeptide muKS1 (SEQ ID NO: 70), and polynucleotides 55-288 of huKS1 (SEQ ID NO: 71), encoding amino acids 19-95 of polypeptide huKS1 (SEQ ID NO: 72), were cloned into the bacterial expression vector pET-16b (Novagen, Madison, WI), which contains a bacterial leader sequence and N-terminal 6xHistidine tag. These constructs were transformed into competent *E. coli* BL21(DE3) (Novagen) as described in Sambrook *et al., Ibid.*

Starter cultures of recombinant *E. coli* BL21(DE3) (Novagen) transformed with bacterial expression vector pET16b containing SEQ ID NO: 69 (muKS1a) and SEQ ID NO: 71 (huKS1a) were grown in NZY broth containing 100 μg/ml ampicillin (Gibco-BRL Life Technologies) at 37°C. Cultures were spun down and used to inoculate 800 ml of NZY broth and 100 μg/ml ampicillin. Cultures were grown until the OD_{595} of the cells was between 0.4 and 0.8. Bacterial expression was induced for 3 hours with 1 mM IPTG. Bacterial expression produced an induced band of approximately 15 kDa for muKS1a and huKS1a.

MuKS1a and huKS1a were expressed in insoluble inclusion bodies. In order to purify the polypeptides, bacterial cell pellets were re-suspended in lysis buffer (20 mM Tris-HCl pH 8.0, 10 mM β–Mercaptoethanol, 1 mM PMSF). To the lysed cells, 1% NP-40 was added and the mix incubated on ice for 10 minutes. Lysates were further disrupted by sonication on ice at 95 W for 4 x 15 seconds and then centrifuged for 10 minutes at 18,000 rpm to pellet the inclusion bodies.

The pellet containing the inclusion bodies was re-suspended in lysis buffer containing 0.5% w/v CHAPS and sonicated for 5-10 seconds. This mix was stored on ice for 1 hour, centrifuged at 14,000 rpm for 15 minutes at 4°C and the supernatant discarded. The pellet was once more re-suspended in lysis buffer

containing 0.5% w/v CHAPS, sonicated, centrifuged and the supernatant removed as before. The pellet was re-suspended in solubilizing buffer (6 M guanidine HCl, 0.5 M NaCl, 20 mM Tris-HCl pH 8.0), sonicated at 95 W for 4 x 15 sec and centrifuged for 10 minutes at 18,000 rpm and 4°C to remove debris. The supernatant was stored at 4°C. MuKS1a and huKS1a were purified by virtue of the N-terminal 6x histidine tag contained within the bacterial leader sequence, using a Nickel-Chelating sepharose column (Amersham Pharmacia, Uppsala, Sweden) and following the manufacturer's protocol. Proteins were purified twice over the column to reduce endotoxin contamination. In order to re-fold the proteins once purified, the protein solution was dialysed in a 4 M-2 M urea gradient in 20 mM Tris-HCl pH 7.5 containing 10% glycerol overnight at 4°C. The protein was then further dialysed 2x against 2 litres of 20 mM Tris-HCl pH 7.5 containing 10% glycerol.

Injection of bacterially expressed muKS1a into nude mice

Two nude mice were anaesthetised intraperitoneally with 75 µl of 1/10 dilution of Hypnorm (Janssen Pharmaceuticals, Buckinghamshire, England) in phosphate buffered saline. 20 µg of bacterially expressed muKS1a (SEQ ID NO: 70) was injected subcutaneously in the left hind foot, ear and left hand side of the back. The same volume of phosphate buffered saline was injected in the same sites but on the right hand side of the same animal. Mice were left for 18 hours and then examined for inflammation. Both mice showed a red swelling in the ear and foot sites injected with the bacterially expressed protein. No obvious inflammation could be identified in either back site. Mice were culled and biopsies taken from the ear, back and foot sites and fixed in 3.7% formol saline. Biopsies were embedded, sectioned and stained with Haemotoxylin and eosin. Sites injected with muKS1a had a marked increase in polymorphonuclear granulocytes, whereas sites injected with phosphate buffered saline had a low background infiltrate of polymorphonuclear granulocytes.

Chemokines are a large superfamily of highly basic secreted proteins with a broad number of functions (Baggiolini *et al.*, *Annu. Rev. Immunol.* 15:675-705, 1997; Ward *et al.*, *Immunity* 9:1-11, 1998; Horuk, *Nature* 393:524-525, 1998). The polypeptide sequences of muKS1 and huKS1 have similarity to CXC chemokines, suggesting that this protein will act like other CXC chemokines. The *in vivo* data from nude mice supports this hypothesis. This chemokine-like protein may therefore be expected to stimulate leukocyte, epithelial, stromal and neuronal cell migration, promote angiogenesis and vascular development, promote neuronal patterning, hematopoietic stem cell mobilization, keratinocyte and epithelial stem cell patterning and development, activation and proliferation of leukocytes, and promotion of migration in wound healing events. It has recently been shown that receptors to chemokines act as co-receptors for HIV-1 infection of CD4+ cells (Cairns *et al.*, *Nature Medicine* 4:563-568, 1998) and that high circulating levels of chemokines can render a degree of immunity to those exposed to the HIV virus (Zagury *et al.*, *Proc. Natl. Acad. Sci. USA* 95:3857-3861, 1998). This novel gene and its encoded protein may thus be usefully employed as regulators of epithelial, lymphoid, myeloid, stromal and neuronal cells migration and cancers; as agents for the treatment of cancers, neuro-degenerative diseases, inflammatory autoimmune diseases such as psoriasis, asthma and Crohns disease; for use in wound healing; and as agents for the prevention of HIV-1 binding and infection of leukocytes.

SEQ ID NOS: 1-72 are set out in the attached Sequence Listing. The codes for nucleotide sequences used in the attached Sequence Listing, including the symbol "n," conform to WIPO Standard ST.25 (1998), Appendix 2, Table 1.

All references cited herein, including patent references and non-patent publications, are hereby incorporated by reference in their entireties.

While in the foregoing specification this invention has been described in relation to certain preferred embodiments, and many details have been set forth for purposes of illustration, it will be apparent to those skilled in the art that the invention is susceptible to additional embodiments and that certain of the details

described herein may be varied considerably without departing from the basic principles of the invention.

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We claim:

1. An isolated polynucleotide comprising a sequence selected from the group consisting of: (1) sequences recited in SEQ ID NOS: 1-35; (2) complements of the sequences recited in SEQ ID NOS: 1-35; (3) reverse complements of the sequences recited in SEQ ID NOS: 1-35; (4) reverse sequences of the sequences recited in SEQ ID NOS: 1-35 (5) sequences having at least a 99% probability of being the same as a sequence recited in (1) – (4) above as determined using computer algorithm BLASTN; (6) sequences having at least 50% identity to a nucleotide sequence recited in (1) – (4) above determined using computer algorithm BLASTN; (7) sequences having at least 75% identity to a nucleotide sequence recited in (1) – (4) above determined using computer algorithm BLASTN; (8) sequences having at least 90% identity to a nucleotide sequence recited in (1) – (4) above determined using computer algorithm BLASTN; (9) sequences having at least 95% identity to a nucleotide sequence recited in (1) – (4) above determined using computer algorithm BLASTN; (10) nucleotide sequences that hybridize to a sequence recited in (1) – (4) above under stringent hybridization conditions; (11) nucleotide sequences that are 200-mers of a sequence recited in (1) – (4) above; (12) nucleotide sequences that are 100-mers of a sequence recited in (1) – (4) above; (13) nucleotide sequences that are 40-mers of a sequence recited in (1) – (4) above; (14) nucleotide sequences that are 20-mers of a sequence recited in (1) – (4) above; and (15) nucleotide sequences that are degeneratively equivalent to a sequence recited in (1) – (4) above.

2. An oligonucleotide comprising at least 10 contiguous residues complementary to 10 contiguous residues of a nucleotide sequence recited in claim 1.

3. A genetic construct comprising an isolated polynucleotide of claim 1.

4. A host cell transformed with a genetic construct of claim 3.

5. An isolated polypeptide encoded by a polynucleotide of claim 1.

6. An isolated polypeptide comprising an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 36-65; (b) sequences having at least a 99% probability of being the same as a sequence of SEQ ID NOS: 36-65, as determined using the computer algorithm BLASTP; (c) sequences having at least 50% identity to a sequence provided in SEQ ID NOS: 36-65, as determined using the computer algorithm BLASTP; (d) sequences having at least 75% identity to a sequence provided in SEQ ID NOS: 36-65, as determined using the computer algorithm BLASTP; (e) sequences having at least 90% identity to a sequence provided in SEQ ID NOS: 36-65, as determined using the computer algorithm BLASTP; and (f) sequences having at least 95% identity to a sequence provided in SEQ ID NOS: 36-65, as determined using the computer algorithm BLASTP.

7. An isolated polynucleotide encoding a polypeptide of claim 6.

8. An isolated polypeptide comprising at least a functional portion of a polypeptide comprising an amino acid sequence selected from the group consisting of: (a) sequences provided in SEQ ID NOS: 36-65; (b) sequences having at least a 99% probability of being the same as a sequence of SEQ ID NOS: 36-65, as determined using the computer algorithm BLASTP; (c) sequences having at least 50% identity to a sequence provided in SEQ ID NOS: 36-65, as determined using the computer algorithm BLASTP; (d) sequences having at least 75% identity to a sequence provided in SEQ ID NOS: 36-65, as determined using the computer algorithm BLASTP; (e) sequences having at least 90% identity to a sequence provided in SEQ ID NOS: 36-65, as determined using the computer algorithm BLASTP and (f) sequences having at least 95% identity to a sequence

provided in SEQ ID NOS: 36-65, as determined using the computer algorithm BLASTP.

9. A composition comprising a polypeptide according to any one of claims 6 and 8 and at least one component selected from the group consisting of: physiologically acceptable carriers and immunostimulants.

10. A composition comprising a polynucleotide according to claim 1 and at least one component selected from the group consisting of pharmaceutically acceptable carriers and immunostimulants.

11. A method for treating a disorder in a mammal comprising administering a composition according to claim 9.

12. A method for treating a disorder in a mammal comprising administering a composition according to claim 10.

13. A diagnostic kit comprising at least one oligonucleotide according to claim 2.

14. An organism comprising a host cell according to claim 4.

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<213> Mouse

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Asp Ser Asp Phe Ser Ala Glu Thr Glu Ala Val Thr Thr Leu Gln Asp
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Val Pro Gly Glu Pro Pro Gly Ser Val Ser Ala Thr Pro His Thr Thr
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Arg Val Val Ala Val Asn Lys Ala Gly Phe Gly Glu Pro Ser Arg Pro
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Val Val Phe Val Leu Val Leu His Gly Gln Ser Lys Lys Tyr Lys Asn
                565                 570                 575
Cys Gly Ser Gly Lys Gly Ile Ser Asn Met Glu Glu Thr Val Thr Leu
            580                 585                 590
Asp Asn Gly Gly Phe Ala Ala Leu Glu Leu Asn Ser Arg His Leu Asn
        595                 600                 605
Val Lys Ser Thr Phe Ser Lys Lys Asn Gly Thr Arg Ser Pro Pro Arg
    610                 615                 620
Pro Ser Pro Gly Gly Leu His Tyr Ser Asp Glu Asp Ile Cys Asn Lys
625                 630                 635                 640
Tyr Asn Gly Ala Val Leu Thr Glu Ser Val Asn Leu Lys Glu Lys Ser
                645                 650                 655
Val Asp Gly Ser Glu Ser Glu Ala Ser Asp Ser Asp Tyr Glu Glu Ala
            660                 665                 670
Leu Pro Lys His Ser Phe Val Asn His Tyr Met Ser Asp Pro Thr Tyr
        675                 680                 685
Tyr Asn Phe Trp Lys Arg Arg Pro Pro Ala Ala Ala Pro His Arg Tyr
    690                 695                 700
Glu Ala Val Ala Gly Ala Glu Ala Gly Pro His Leu His Thr Val Ile
705                 710                 715                 720
Thr Thr Gln Ser Ala Gly Gly Val Tyr Thr Pro Ala Gly Pro Gly Ala
                725                 730                 735
Arg Ala Pro Leu Thr Gly Phe Ser Ser Phe Val
            740                 745
```

<210> 37
<211> 205
<212> PRT
<213> Mouse

<400> 37

```
Met Leu Gly Thr Leu Val Trp Met Leu Ala Val Gly Phe Leu Leu Ala
 1                5                  10                  15
Leu Ala Pro Gly Arg Ala Ala Gly Ala Leu Arg Thr Gly Arg Arg Pro
            20                  25                  30
Ala Arg Pro Arg Asp Cys Ala Asp Arg Pro Glu Glu Leu Leu Glu Gln
        35                  40                  45
Leu Tyr Gly Arg Leu Ala Ala Gly Val Leu Ser Ala Phe His His Thr
    50                  55                  60
Leu Gln Leu Gly Pro Arg Glu Gln Ala Arg Asn Ala Ser Cys Pro Ala
65                  70                  75                  80
Gly Gly Arg Ala Ala Asp Arg Arg Phe Arg Pro Pro Thr Asn Leu Arg
                85                  90                  95
Ser Val Ser Pro Trp Ala Tyr Arg Ile Ser Tyr Asp Pro Ala Arg Phe
            100                 105                 110
```

```
Pro Arg Tyr Leu Pro Glu Ala Tyr Cys Leu Cys Arg Gly Cys Leu Thr
        115                 120                 125
Gly Leu Tyr Gly Glu Glu Asp Phe Arg Phe Arg Ser Thr Pro Val Phe
    130                 135                 140
Ser Pro Ala Val Val Leu Arg Arg Thr Ala Ala Cys Ala Gly Gly Arg
145                 150                 155                 160
Ser Val Tyr Ala Glu His Tyr Ile Thr Ile Pro Val Gly Cys Thr Cys
                165                 170                 175
Val Pro Glu Pro Asp Lys Ser Ala Asp Ser Ala Asn Ser Ser Met Asp
            180                 185                 190
Lys Leu Leu Leu Gly Pro Ala Asp Arg Pro Ala Gly Arg
        195                 200                 205
```

<210> 38
<211> 238
<212> PRT
<213> Mouse

<400> 38

```
Met Leu Cys Phe Leu Arg Gly Met Ala Phe Val Pro Phe Leu Leu Val
 1               5                  10                  15
Thr Trp Ser Ser Ala Ala Phe Ile Ile Ser Tyr Val Val Ala Val Leu
            20                  25                  30
Ser Gly His Val Asn Pro Phe Leu Pro Tyr Ile Ser Asp Thr Gly Thr
        35                  40                  45
Thr Pro Pro Glu Ser Gly Ile Phe Gly Phe Met Ile Asn Phe Ser Ala
    50                  55                  60
Phe Leu Gly Ala Ala Thr Met Tyr Thr Arg Tyr Lys Ile Val Glu Lys
65                  70                  75                  80
Gln Asn Glu Thr Cys Tyr Phe Ser Thr Pro Val Phe Asn Leu Val Ser
                85                  90                  95
Leu Ala Leu Gly Leu Val Gly Cys Ile Gly Met Gly Ile Val Ala Asn
            100                 105                 110
Phe Gln Glu Leu Ala Val Pro Val Val His Asp Gly Gly Ala Leu Leu
        115                 120                 125
Ala Phe Val Cys Gly Val Val Tyr Thr Leu Leu Gln Ser Ile Ile Ser
    130                 135                 140
Tyr Lys Ser Cys Pro Gln Trp Asn Ser Leu Thr Thr Cys His Val Arg
145                 150                 155                 160
Met Ala Ile Ser Ala Val Ser Cys Ala Ala Val Val Pro Met Ile Ala
                165                 170                 175
Cys Ala Ser Leu Ile Ser Ile Thr Lys Leu Glu Trp Asn Pro Lys Glu
            180                 185                 190
Lys Asp Tyr Ile Tyr His Val Val Ser Ala Ile Cys Glu Trp Thr Val
        195                 200                 205
Ala Phe Gly Phe Ile Phe Tyr Phe Leu Thr Phe Ile Gln Asp Phe Gln
    210                 215                 220
Ser Val Thr Leu Arg Ile Ser Thr Glu Ile Asn Asp Asp Phe
225                 230                 235
```

<210> 39
<211> 492
<212> PRT
<213> Mouse

<400> 39

```
Leu Arg Leu Leu Leu Ala Trp Val Ala Ala Val Pro Ala Leu Gly Gln
```

```
 1               5                  10                  15
Val Pro Trp Thr Pro Glu Pro Arg Ala Ala Cys Gly Pro Ser Ser Cys
            20                  25                  30
Tyr Ala Leu Phe Pro Arg Arg Arg Thr Phe Leu Glu Ala Trp Arg Ala
        35                  40                  45
Cys Arg Glu Leu Gly Gly Asn Leu Ala Thr Pro Arg Thr Pro Glu Glu
    50                  55                  60
Ala Gln Arg Val Asp Ser Leu Val Gly Val Gly Pro Ala Asn Gly Leu
65                  70                  75                  80
Leu Trp Ile Gly Leu Gln Arg Gln Ala Arg Gln Cys Gln Pro Gln Arg
                85                  90                  95
Pro Leu Arg Gly Phe Ile Trp Thr Thr Gly Asp Gln Asp Thr Ala Phe
            100                 105                 110
Thr Asn Trp Ala Gln Pro Ala Thr Glu Gly Pro Cys Pro Ala Gln Arg
        115                 120                 125
Cys Ala Ala Leu Glu Ala Ser Gly Glu His Arg Trp Leu Glu Gly Ser
    130                 135                 140
Cys Thr Leu Ala Val Asp Gly Tyr Leu Cys Gln Phe Gly Phe Glu Gly
145                 150                 155                 160
Ala Cys Pro Ala Leu Pro Leu Glu Val Gly Gln Ala Gly Pro Ala Val
                165                 170                 175
Tyr Thr Thr Pro Phe Asn Leu Val Ser Ser Glu Phe Glu Trp Leu Pro
            180                 185                 190
Phe Gly Ser Val Ala Ala Val Gln Cys Gln Ala Gly Arg Gly Ala Ser
        195                 200                 205
Leu Leu Cys Val Lys Gln Pro Ser Gly Gly Val Gly Trp Ser Gln Thr
    210                 215                 220
Gly Pro Leu Cys Pro Gly Thr Gly Cys Gly Pro Asp Asn Gly Gly Cys
225                 230                 235                 240
Glu His Glu Cys Val Glu Glu Val Asp Gly Ala Val Ser Cys Arg Cys
                245                 250                 255
Ser Glu Gly Phe Arg Leu Ala Ala Asp Gly His Ser Cys Glu Asp Pro
            260                 265                 270
Cys Ala Gln Ala Pro Cys Glu Gln Gln Cys Glu Pro Gly Gly Pro Gln
        275                 280                 285
Gly Tyr Ser Cys His Cys Arg Leu Gly Phe Arg Pro Ala Glu Asp Asp
    290                 295                 300
Pro His Arg Cys Val Asp Thr Asp Glu Cys Gln Ile Ala Gly Val Cys
305                 310                 315                 320
Gln Gln Met Cys Val Asn Tyr Val Gly Gly Phe Glu Cys Tyr Cys Ser
                325                 330                 335
Glu Gly His Glu Leu Glu Ala Asp Gly Ile Ser Cys Ser Pro Ala Gly
            340                 345                 350
Ala Met Gly Ala Gln Ala Ser Gln Asp Leu Arg Asp Glu Leu Leu Asp
        355                 360                 365
Asp Gly Glu Glu Gly Glu Asp Glu Glu Glu Pro Trp Glu Asp Phe Asp
    370                 375                 380
Gly Thr Trp Thr Glu Glu Gln Gly Ile Leu Trp Leu Ala Pro Thr His
385                 390                 395                 400
Pro Pro Asp Phe Gly Leu Pro Tyr Arg Pro Asn Phe Pro Gln Asp Gly
                405                 410                 415
Glu Pro Gln Arg Leu His Leu Glu Pro Thr Trp Pro Pro Pro Leu Lys
            420                 425                 430
Ala Pro Lys Gly Pro Gln Gln Pro Pro Arg Gly Ala Ala Lys Thr Pro
        435                 440                 445
Lys Gly Asn Pro Ala Asn Pro Thr His Thr Thr Phe Cys Pro Gln Asp
    450                 455                 460
```

```
Leu Cys Tyr Phe Ser Tyr Thr Pro Thr Pro Glu Pro Cys Pro Pro Thr
465                 470                 475                 480
Cys His Gly Pro Cys His Thr Ser Ser Cys Val Leu
                485                 490
```

<210> 40
<211> 464
<212> PRT
<213> Mouse

<400> 40

```
Met Gly Arg Ala Trp Gly Leu Leu Val Gly Leu Leu Gly Val Val Trp
 1               5                  10                  15
Leu Leu Arg Leu Gly His Gly Glu Glu Arg Arg Pro Glu Thr Ala Ala
            20                  25                  30
Gln Arg Cys Phe Cys Gln Val Ser Gly Tyr Leu Asp Asp Cys Thr Cys
        35                  40                  45
Asp Val Glu Thr Ile Asp Lys Phe Asn Asn Tyr Arg Leu Phe Pro Arg
    50                  55                  60
Leu Gln Lys Leu Leu Glu Ser Asp Tyr Phe Arg Tyr Tyr Lys Val Asn
65                  70                  75                  80
Leu Lys Lys Pro Cys Pro Phe Trp Asn Asp Ile Asn Gln Cys Gly Arg
                85                  90                  95
Arg Asp Cys Ala Val Lys Pro Cys His Ser Asp Glu Val Pro Asp Gly
            100                 105                 110
Ile Lys Ser Ala Ser Tyr Lys Tyr Ser Glu Glu Ala Asn Arg Ile Glu
        115                 120                 125
Glu Cys Glu Gln Ala Glu Arg Leu Gly Ala Val Asp Glu Ser Leu Ser
    130                 135                 140
Glu Glu Thr Gln Lys Ala Val Leu Gln Trp Thr Lys His Asp Asp Ser
145                 150                 155                 160
Ser Asp Ser Phe Cys Glu Ile Asp Asp Ile Gln Ser Pro Asp Ala Glu
                165                 170                 175
Tyr Val Asp Leu Leu Leu Asn Pro Glu Arg Tyr Thr Gly Tyr Lys Gly
            180                 185                 190
Pro Asp Ala Trp Arg Ile Trp Ser Val Ile Tyr Glu Glu Asn Cys Phe
        195                 200                 205
Lys Pro Gln Thr Ile Gln Arg Pro Leu Ala Ser Gly Arg Gly Lys Ser
    210                 215                 220
Lys Glu Asn Thr Phe Tyr Asn Trp Leu Glu Gly Leu Cys Val Glu Lys
225                 230                 235                 240
Arg Ala Phe Tyr Arg Leu Ile Ser Gly Leu His Ala Ser Ile Asn Val
                245                 250                 255
His Leu Ser Ala Arg Tyr Leu Leu Gln Asp Thr Trp Leu Glu Lys Lys
            260                 265                 270
Trp Gly His Asn Val Thr Glu Phe Gln Gln Arg Phe Asp Gly Ile Leu
        275                 280                 285
Thr Glu Gly Glu Gly Pro Arg Arg Leu Arg Asn Leu Tyr Phe Leu Tyr
    290                 295                 300
Leu Ile Glu Leu Arg Ala Leu Ser Lys Val Leu Pro Phe Phe Glu Arg
305                 310                 315                 320
Pro Asp Phe Gln Leu Phe Thr Gly Asn Lys Val Gln Asp Ala Glu Asn
                325                 330                 335
Lys Ala Leu Leu Leu Glu Ile Leu His Glu Ile Lys Ser Phe Pro Leu
            340                 345                 350
His Phe Asp Glu Asn Ser Phe Phe Ala Gly Asp Lys Asn Glu Ala His
        355                 360                 365
```

```
Lys Leu Lys Glu Asp Phe Arg Leu His Phe Arg Asn Ile Ser Arg Ile
    370                 375                 380
Met Asp Cys Val Gly Cys Phe Lys Cys Arg Leu Trp Gly Lys Leu Gln
385                 390                 395                 400
Thr Gln Gly Leu Gly Thr Ala Leu Lys Ile Leu Phe Ser Glu Lys Leu
                405                 410                 415
Ile Ala Asn Met Pro Glu Ser Gly Pro Ser Tyr Glu Phe Gln Leu Thr
            420                 425                 430
Arg Gln Glu Ile Val Ser Leu Phe Asn Ala Phe Gly Arg Ile Ser Thr
        435                 440                 445
Ser Val Arg Glu Leu Glu Asn Phe Arg His Leu Leu Gln Asn Val His
    450                 455                 460
```

<210> 41
<211> 148
<212> PRT
<213> Rat

<400> 41

```
Leu Asn Trp Gln Ile Lys Lys Tyr Asp Thr Lys Ala Ala Tyr Cys Gln
 1               5                  10                  15
Ser Lys Leu Ala Val Val Leu Phe Thr Lys Glu Leu Ser Arg Arg Leu
            20                  25                  30
Gln Gly Thr Gly Val Thr Val Asn Ala Leu His Pro Gly Val Ala Arg
        35                  40                  45
Thr Glu Leu Gly Arg His Thr Gly Met His Asn Ser Ala Phe Ser Gly
    50                  55                  60
Phe Met Leu Gly Pro Phe Phe Trp Leu Leu Phe Lys Ser Pro Gln Leu
65                  70                  75                  80
Ala Ala Gln Pro Ser Thr Tyr Leu Ala Val Ala Glu Glu Leu Glu Ser
                85                  90                  95
Val Ser Gly Lys Tyr Phe Asp Gly Leu Arg Glu Lys Ala Pro Ser Pro
            100                 105                 110
Glu Ala Glu Asp Glu Glu Val Ala Arg Arg Leu Trp Thr Glu Ser Ala
        115                 120                 125
His Leu Val Gly Leu Asp Met Ala His Gly Ser Ser Gly Arg Gly His
    130                 135                 140
Ser Ile Ser Arg
145
```

<210> 42
<211> 228
<212> PRT
<213> Mouse

<400> 42

```
Met Gly Phe Leu Leu Leu Leu Leu Leu His Ala Ala Ile Ala Gly His
 1               5                  10                  15
Lys Asn Tyr Gly Thr His Asn His Cys Trp Leu Ser Leu His Arg Gly
            20                  25                  30
Phe Ile Trp Ser Phe Leu Gly Pro Ala Ala Ala Ile Ile Leu Ile Asn
        35                  40                  45
Leu Val Phe Tyr Phe Leu Ile Ile Trp Ile Leu Arg Ser Lys Leu Ser
    50                  55                  60
Ser Leu Asn Lys Glu Val Ser Thr Leu Gln Asp Thr Lys Val Met Thr
65                  70                  75                  80
Phe Lys Ala Ile Val Gln Leu Phe Val Leu Gly Cys Ser Trp Gly Ile
```

85 90 95
Gly Leu Phe Ile Phe Ile Glu Val Gly Lys Thr Val Arg Leu Ile Val
100 105 110
Ala Tyr Leu Phe Thr Ile Ile Asn Val Leu Gln Gly Val Leu Ile Phe
115 120 125
Met Val His Cys Leu Leu Asn Arg Gln Val Arg Met Glu Tyr Lys Lys
130 135 140
Trp Phe His Arg Leu Arg Lys Glu Val Glu Ser Glu Ser Thr Glu Val
145 150 155 160
Ser His Ser Thr Thr His Thr Lys Met Gly Leu Ser Leu Asn Leu Glu
165 170 175
Asn Phe Cys Pro Thr Gly Asn Leu His Asp Pro Ser Asp Ser Ile Leu
180 185 190
Pro Ser Thr Glu Val Ala Gly Val Tyr Leu Ser Thr Pro Arg Ser His
195 200 205
Met Gly Ala Glu Asp Val Asn Ser Gly Thr His Ala Tyr Trp Ser Arg
210 215 220
Thr Ile Ser Asp
225

<210> 43
<211> 373
<212> PRT
<213> Mouse

<400> 43
Met Lys Glu Tyr Val Met Leu Leu Leu Leu Ala Val Cys Ser Ala Lys
1 5 10 15
Pro Phe Phe Ser Pro Ser His Thr Ala Leu Lys Asn Met Met Leu Lys
20 25 30
Asp Met Glu Asp Thr Asp Asp Asp Asp Asn Asp Asp Asp Asp Asn Ser
35 40 45
Leu Phe Pro Thr Lys Glu Pro Val Asn Pro Phe Phe Pro Phe Asp Leu
50 55 60
Phe Pro Thr Cys Pro Phe Gly Cys Gln Cys Tyr Ser Arg Val Val His
65 70 75 80
Cys Ser Asp Leu Gly Leu Thr Ser Val Pro Asn Asn Ile Pro Phe Asp
85 90 95
Thr Arg Met Val Asp Leu Gln Asn Asn Lys Ile Lys Glu Ile Lys Glu
100 105 110
Asn Asp Phe Lys Gly Leu Thr Ser Leu Tyr Ala Leu Ile Leu Asn Asn
115 120 125
Asn Lys Leu Thr Lys Ile His Pro Lys Thr Phe Leu Thr Thr Lys Lys
130 135 140
Leu Arg Arg Leu Tyr Leu Ser His Asn Gln Leu Ser Glu Ile Pro Leu
145 150 155 160
Asn Leu Pro Lys Ser Leu Ala Glu Leu Arg Ile His Asp Asn Lys Val
165 170 175
Lys Lys Ile Gln Lys Asp Thr Phe Lys Gly Met Asn Ala Leu His Val
180 185 190
Leu Glu Met Ser Ala Asn Pro Leu Glu Asn Asn Gly Ile Glu Pro Gly
195 200 205
Ala Phe Glu Gly Val Thr Val Phe His Ile Arg Ile Ala Glu Ala Lys
210 215 220
Leu Thr Ser Ile Pro Lys Gly Leu Pro Pro Thr Leu Leu Glu Leu His
225 230 235 240
Leu Asp Phe Asn Lys Ile Ser Thr Val Glu Leu Glu Asp Leu Lys Arg

245 250 255
Tyr Arg Glu Leu Gln Arg Leu Gly Leu Gly Asn Asn Arg Ile Thr Asp
260 265 270
Ile Glu Asn Gly Thr Phe Ala Asn Ile Pro Arg Val Arg Glu Ile His
275 280 285
Leu Glu His Asn Lys Leu Lys Lys Ile Pro Ser Gly Leu Gln Glu Leu
290 295 300
Lys Tyr Leu Gln Ile Ile Phe Leu His Tyr Asn Ser Ile Ala Lys Val
305 310 315 320
Gly Val Asn Asp Phe Cys Pro Thr Val Pro Lys Met Lys Lys Ser Leu
325 330 335
Tyr Ser Ala Ile Ser Leu Phe Asn Asn Pro Met Lys Tyr Trp Glu Ile
340 345 350
Gln Pro Ala Thr Phe Arg Cys Val Leu Gly Arg Met Ser Val Gln Leu
355 360 365
Gly Asn Val Gly Lys
370

<210> 44
<211> 466
<212> PRT
<213> Mouse

<400> 44
Met Trp Gly Cys Trp Leu Gly Leu Leu Leu Leu Leu Leu Ala Gly Gln
1 5 10 15
Ala Ala Leu Glu Ala Arg Arg Ser Arg Trp Arg Arg Glu Leu Ala Pro
20 25 30
Gly Leu His Leu Arg Gly Ile Arg Asp Ala Gly Gly Arg Tyr Cys Gln
35 40 45
Glu Gln Asp Met Cys Cys Arg Gly Arg Ala Asp Glu Cys Ala Leu Pro
50 55 60
Tyr Leu Gly Ala Thr Cys Tyr Cys Asp Leu Phe Cys Asn Arg Thr Val
65 70 75 80
Ser Asp Cys Cys Pro Asp Phe Trp Asp Phe Cys Leu Gly Ile Pro Pro
85 90 95
Pro Phe Pro Pro Val Gln Gly Cys Met His Gly Gly Arg Ile Tyr Pro
100 105 110
Val Phe Gly Thr Tyr Trp Asp Asn Cys Asn Arg Cys Thr Cys His Glu
115 120 125
Gly Gly His Trp Glu Cys Asp Gln Glu Pro Cys Leu Val Asp Pro Asp
130 135 140
Met Ile Lys Ala Ile Asn Arg Gly Asn Tyr Gly Trp Gln Ala Gly Asn
145 150 155 160
His Ser Ala Phe Trp Gly Met Thr Leu Asp Glu Gly Ile Arg Tyr Arg
165 170 175
Leu Gly Thr Ile Arg Pro Ser Ser Thr Val Met Asn Met Asn Glu Ile
180 185 190
Tyr Thr Val Leu Gly Gln Gly Glu Val Leu Pro Thr Ala Phe Glu Ala
195 200 205
Ser Glu Lys Trp Pro Asn Leu Ile His Glu Pro Leu Asp Gln Gly Asn
210 215 220
Cys Ala Gly Ser Trp Ala Phe Ser Thr Ala Ala Val Ala Ser Asp Arg
225 230 235 240
Val Ser Ile His Ser Leu Gly His Met Thr Pro Ile Leu Ser Pro Gln
245 250 255
Asn Leu Leu Ser Cys Asp Thr His His Gln Gln Gly Cys Arg Gly Gly

```
            260                 265                 270
Arg Leu Asp Gly Ala Trp Trp Phe Leu Arg Arg Arg Gly Val Val Ser
        275                 280                 285
Asp Asn Cys Tyr Pro Phe Ser Gly Arg Glu Gln Asn Glu Ala Ser Pro
    290                 295                 300
Thr Pro Arg Cys Met Met His Ser Arg Ala Met Gly Arg Gly Lys Arg
305                 310                 315                 320
Gln Ala Thr Ser Arg Cys Pro Asn Gly Gln Val Asp Ser Asn Asp Ile
                325                 330                 335
Tyr Gln Val Thr Pro Ala Tyr Arg Leu Gly Ser Asp Glu Lys Glu Ile
            340                 345                 350
Met Lys Glu Leu Met Glu Asn Gly Pro Val Gln Ala Leu Met Glu Val
        355                 360                 365
His Glu Asp Phe Phe Leu Tyr Gln Arg Gly Ile Tyr Ser His Thr Pro
    370                 375                 380
Val Ser Gln Gly Arg Pro Glu Gln Tyr Arg Arg His Gly Thr His Ser
385                 390                 395                 400
Val Lys Ile Thr Gly Trp Gly Glu Glu Thr Leu Pro Asp Gly Arg Thr
                405                 410                 415
Ile Lys Tyr Trp Thr Ala Ala Asn Ser Trp Gly Pro Trp Trp Gly Glu
            420                 425                 430
Arg Gly His Phe Arg Ile Val Arg Gly Thr Asn Glu Cys Asp Ile Glu
        435                 440                 445
Thr Phe Val Leu Gly Val Trp Gly Arg Val Gly Met Glu Asp Met Gly
    450                 455                 460
His His
465
```

<210> 45
<211> 422
<212> PRT
<213> Mouse

<400> 45

```
Met Asp Phe Trp Leu Trp Leu Leu Tyr Phe Leu Pro Val Ser Gly Ala
 1               5                  10                  15
Leu Arg Val Leu Pro Glu Val Gln Leu Asn Val Glu Trp Gly Gly Ser
            20                  25                  30
Ile Ile Ile Glu Cys Pro Leu Pro Gln Leu His Val Arg Met Tyr Leu
        35                  40                  45
Cys Arg Gln Met Ala Lys Pro Gly Ile Cys Ser Thr Val Val Ser Asn
    50                  55                  60
Thr Phe Val Lys Lys Glu Tyr Glu Arg Arg Val Thr Leu Thr Pro Cys
65                  70                  75                  80
Leu Asp Lys Lys Leu Phe Leu Val Glu Met Thr Gln Leu Thr Glu Asn
                85                  90                  95
Asp Asp Gly Ile Tyr Ala Cys Gly Val Gly Met Lys Thr Asp Lys Gly
            100                 105                 110
Lys Thr Gln Lys Ile Thr Leu Asn Val His Asn Glu Tyr Pro Glu Pro
        115                 120                 125
Phe Trp Glu Asp Glu Trp Thr Ser Glu Arg Pro Arg Trp Leu His Arg
    130                 135                 140
Phe Leu Gln His Gln Met Pro Trp Leu His Gly Ser Glu His Pro Ser
145                 150                 155                 160
Ser Ser Gly Val Ile Ala Lys Val Thr Thr Pro Ala Ser Lys Thr Glu
                165                 170                 175
Ala Pro Pro Val His Gln Pro Ser Ser Ile Thr Ser Val Thr Gln His
```

```
            180                 185                 190
Pro Arg Val Tyr Arg Ala Phe Ser Val Ser Ala Thr Lys Ser Pro Ala
        195                 200                 205
Leu Leu Pro Ala Thr Thr Ala Ser Lys Thr Ser Thr Gln Gln Ala Ile
    210                 215                 220
Arg Pro Leu Glu Ala Ser Tyr Ser His His Thr Arg Leu His Glu Gln
225                 230                 235                 240
Arg Thr Arg His His Gly Pro His Tyr Gly Arg Glu Asp Arg Gly Leu
                245                 250                 255
His Ile Pro Ile Pro Glu Phe His Ile Leu Ile Pro Thr Phe Leu Gly
            260                 265                 270
Phe Leu Leu Leu Val Leu Leu Gly Leu Val Val Lys Arg Ala Ile Gln
        275                 280                 285
Arg Arg Arg Ala Ser Ser Arg Arg Ala Gly Arg Leu Ala Met Arg Arg
    290                 295                 300
Arg Gly Arg Gly Ala Ser Arg Pro Phe Pro Thr Gln Arg Arg Asp Ala
305                 310                 315                 320
Pro Gln Arg Pro Arg Ser Gln Asn Asn Val Tyr Ser Ala Cys Pro Arg
                325                 330                 335
Arg Ala Arg Gly Pro Asp Ser Leu Gly Pro Ala Glu Ala Pro Leu Leu
            340                 345                 350
Asn Ala Pro Ala Ser Ala Ser Pro Ala Ser Pro Gln Val Leu Glu Ala
        355                 360                 365
Pro Trp Pro His Thr Pro Ser Leu Lys Met Ser Cys Glu Tyr Val Ser
    370                 375                 380
Leu Gly Tyr Gln Pro Ala Val Asn Leu Glu Asp Pro Asp Ser Asp Asp
385                 390                 395                 400
Tyr Ile Asn Ile Pro Asp Pro Ser His Leu Pro Ser Tyr Ala Pro Gly
                405                 410                 415
Pro Arg Ser Ser Cys Gln
            420
```

<210> 46
<211> 228
<212> PRT
<213> Mouse

<400> 46

```
Met Lys Ala Leu Arg Ala Val Leu Leu Ile Leu Leu Leu Ser Gly Gln
 1               5                  10                  15
Pro Gly Ser Gly Trp Ala Gln Glu Asp Gly Asp Ala Asp Pro Glu Pro
            20                  25                  30
Glu Asn Tyr Asn Tyr Asp Asp Asp Asp Asp Glu Glu Glu Glu Glu Glu
        35                  40                  45
Thr Asn Met Ile Pro Gly Ser Arg Asp Arg Ala Pro Leu Gln Cys Tyr
    50                  55                  60
Phe Cys Gln Val Leu His Ser Gly Glu Ser Cys Asn Gln Thr Gln Ser
65                  70                  75                  80
Cys Ser Ser Ser Lys Pro Phe Cys Ile Thr Leu Val Ser His Ser Gly
                85                  90                  95
Thr Asp Lys Gly Tyr Leu Thr Thr Tyr Ser Met Trp Cys Thr Asp Thr
            100                 105                 110
Cys Gln Pro Ile Ile Lys Thr Val Gly Gly Thr Gln Met Thr Gln Thr
        115                 120                 125
Cys Cys Gln Ser Thr Leu Cys Asn Ile Pro Pro Trp Gln Asn Pro Gln
    130                 135                 140
Val Gln Asn Pro Leu Gly Gly Arg Ala Asp Ser Pro Leu Glu Ser Gly
```

145 150 155 160
Thr Arg His Pro Gln Gly Gly Lys Phe Ser His Pro Gln Val Val Lys
165 170 175
Ala Ala His Pro Gln Ser Asp Gly Ala Asn Leu Pro Lys Ser Gly Lys
180 185 190
Ala Asn Gln Pro Gln Gly Ser Gly Ala Gly Tyr Pro Ser Gly Trp Thr
195 200 205
Lys Phe Gly Asn Ile Ala Leu Leu Leu Ser Phe Phe Thr Cys Leu Trp
210 215 220
Ala Ser Gly Ala
225

<210> 47
<211> 269
<212> PRT
<213> Mouse

<400> 47
Gly Cys Ser Asp Gly Glu Asn Gln Arg Ser Gly His Leu Ser Val Ser
1 5 10 15
Leu Gln Leu Ser Leu Lys Val Leu Leu Ile Arg Met Ala Ser Gly Trp
20 25 30
Phe Tyr Leu Ser Cys Met Val Leu Gly Ser Leu Gly Ser Met Cys Ile
35 40 45
Leu Phe Thr Ala Tyr Trp Met Gln Tyr Trp Arg Gly Gly Phe Ala Trp
50 55 60
Asp Gly Thr Val Leu Met Phe Asn Trp His Pro Val Leu Met Val Ala
65 70 75 80
Gly Met Val Val Leu Tyr Gly Ala Ala Ser Leu Val Tyr Arg Leu Pro
85 90 95
Ser Ser Trp Val Gly Pro Arg Leu Pro Trp Lys Val Leu His Ala Ala
100 105 110
Leu His Leu Leu Ala Phe Thr Cys Thr Val Val Gly Leu Ile Ala Val
115 120 125
Phe Arg Phe His Asn His Ser Arg Ile Ala His Leu Tyr Ser Leu His
130 135 140
Ser Trp Leu Gly Ile Thr Thr Val Val Leu Phe Ala Cys Gln Trp Phe
145 150 155 160
Leu Gly Phe Ala Val Phe Leu Leu Pro Trp Ala Ser Gln Trp Leu Arg
165 170 175
Ser Leu Leu Lys Pro Leu His Val Phe Phe Gly Ala Cys Ile Leu Ser
180 185 190
Leu Ser Ile Thr Ser Val Ile Ser Gly Ile Asn Glu Lys Leu Phe Phe
195 200 205
Val Leu Lys Asn Ala Thr Lys Pro Tyr Ser Ser Leu Pro Gly Glu Ala
210 215 220
Val Phe Ala Asn Ser Thr Gly Leu Leu Val Val Ala Phe Gly Leu Leu
225 230 235 240
Val Leu Tyr Val Leu Leu Ala Ser Ser Trp Lys Arg Pro Asp Pro Gly
245 250 255
Ala Leu Thr Asp Arg Gln Pro Leu Leu His Asp Arg Glu
260 265

<210> 48
<211> 188
<212> PRT
<213> Mouse

<400> 48
Met Arg Leu Pro Leu Pro Leu Leu Leu Leu Phe Gly Cys Arg Ala Ile
1 5 10 15
Leu Gly Ser Ala Gly Asp Arg Val Ser Leu Ser Ala Ser Ala Pro Thr
20 25 30
Leu Asp Asp Glu Glu Lys Tyr Ser Ala His Met Pro Ala His Leu Arg
35 40 45
Cys Asp Ala Cys Arg Ala Val Ala Phe Gln Met Gly Gln Arg Leu Ala
50 55 60
Lys Ala Glu Ala Lys Ser His Thr Pro Asp Ala Ser Gly Leu Gln Glu
65 70 75 80
Leu Ser Glu Ser Thr Tyr Thr Asp Val Leu Asp Gln Thr Cys Ser Gln
85 90 95
Asn Trp Gln Ser Tyr Gly Val His Glu Val Asn Gln Met Lys Arg Leu
100 105 110
Thr Gly Pro Gly Leu Ser Lys Gly Pro Glu Pro Arg Ile Ser Val Met
115 120 125
Ile Ser Gly Gly Pro Trp Pro Asn Arg Leu Ser Lys Thr Cys Phe His
130 135 140
Tyr Leu Gly Glu Phe Gly Glu Asp Gln Ile Tyr Glu Ala Tyr Arg Gln
145 150 155 160
Gly Gln Ala Asn Leu Glu Ala Leu Leu Cys Gly Gly Thr His Gly Pro
165 170 175
Cys Ser Gln Glu Ile Leu Ala Gln Arg Glu Glu Leu
180 185

<210> 49
<211> 247
<212> PRT
<213> Mouse

<400> 49
Met Ile Pro Gln Val Val Thr Ser Glu Thr Val Thr Val Ile Ser Pro
1 5 10 15
Asn Gly Ile Ser Phe Pro Gln Thr Asp Lys Pro Gln Pro Ser His Gln
20 25 30
Ser Gln Asp Arg Leu Lys Lys His Leu Lys Ala Glu Ile Lys Val Met
35 40 45
Ala Ala Ile Gln Ile Met Cys Ala Val Met Val Leu Ser Leu Gly Ile
50 55 60
Ile Leu Ala Ser Val Pro Ser Asn Leu His Phe Thr Ser Val Phe Ser
65 70 75 80
Ile Leu Leu Glu Ser Gly Tyr Pro Phe Val Gly Ala Leu Phe Phe Ala
85 90 95
Ile Ser Gly Ile Leu Ser Ile Val Thr Glu Lys Lys Met Thr Lys Pro
100 105 110
Leu Val His Ser Ser Leu Ala Leu Ser Ile Leu Ser Val Leu Ser Ala
115 120 125
Leu Thr Gly Ile Ala Ile Leu Ser Val Ser Leu Ala Ala Leu Glu Pro
130 135 140
Ala Leu Gln Gln Cys Lys Leu Ala Phe Thr Gln Leu Asp Thr Thr Gln
145 150 155 160
Asp Ala Tyr His Phe Phe Ser Pro Glu Pro Leu Asn Ser Cys Phe Val
165 170 175
Ala Lys Ala Ala Leu Thr Gly Val Phe Ser Leu Met Leu Ile Ser Ser
180 185 190

Val Leu Glu Leu Gly Leu Ala Val Leu Thr Ala Thr Leu Trp Trp Lys
195 200 205
Gln Ser Ser Ser Ala Phe Ser Gly Asn Val Ile Phe Leu Ser Gln Asn
210 215 220
Ser Lys Asn Lys Ser Ser Val Ser Ser Glu Ser Leu Cys Asn Pro Thr
225 230 235 240
Tyr Glu Asn Ile Leu Thr Ser
245

<210> 50
<211> 182
<212> PRT
<213> Mouse

<400> 50
Pro Phe His Cys His Val Trp Ser Leu Cys Leu Gln Gly Ser Lys Gln
1 5 10 15
Ser Gly Leu Cys Gln Val Gln Arg Asp Leu Gly Arg Asp Asp Arg Ser
20 25 30
Val Arg Gly Ser Lys Ala Ala Val Val Ala Gly Ala Val Val Gly Thr
35 40 45
Phe Val Gly Leu Val Leu Ile Ala Gly Leu Val Leu Leu Tyr Gln Arg
50 55 60
Arg Ser Lys Thr Leu Glu Glu Leu Ala Asn Asp Ile Lys Glu Asp Ala
65 70 75 80
Ile Ala Pro Arg Thr Leu Pro Trp Thr Lys Gly Ser Asp Thr Ile Ser
85 90 95
Lys Asn Gly Thr Leu Ser Ser Val Thr Ser Ala Arg Ala Leu Arg Pro
100 105 110
Pro Lys Ala Ala Pro Pro Arg Pro Gly Thr Phe Thr Pro Thr Pro Ser
115 120 125
Val Ser Ser Gln Ala Leu Ser Ser Pro Arg Leu Pro Arg Val Asp Glu
130 135 140
Pro Pro Pro Gln Ala Val Ser Leu Thr Pro Gly Gly Val Ser Ser Ser
145 150 155 160
Ala Leu Ser Arg Met Gly Ala Val Pro Val Met Val Pro Ala Gln Ser
165 170 175
Gln Ala Gly Ser Leu Val
180

<210> 51
<211> 248
<212> PRT
<213> Mouse

<400> 51
Met Ser Trp Ser Pro Ile Leu Pro Phe Leu Ser Leu Leu Leu Leu Leu
1 5 10 15
Phe Pro Leu Glu Val Pro Arg Ala Ala Thr Ala Ser Leu Ser Gln Ala
20 25 30
Ser Ser Glu Gly Thr Thr Thr Cys Lys Val His Asp Val Cys Leu Leu
35 40 45
Gly Pro Arg Pro Leu Pro Pro Ser Pro Pro Val Arg Val Ser Leu Tyr
50 55 60
Tyr Glu Ser Leu Cys Gly Ala Cys Arg Tyr Phe Leu Val Arg Asp Leu
65 70 75 80
Phe Pro Thr Trp Leu Met Val Met Glu Ile Met Asn Ile Thr Leu Val

```
                85                  90                  95
Pro Tyr Gly Asn Ala Gln Glu Arg Asn Val Ser Gly Thr Trp Glu Phe
            100                 105                 110
Thr Cys Gln His Gly Glu Leu Glu Cys Arg Leu Asn Met Val Glu Ala
        115                 120                 125
Cys Leu Leu Asp Lys Leu Glu Lys Glu Ala Ala Phe Leu Thr Ile Val
    130                 135                 140
Cys Met Glu Glu Met Asp Asp Met Glu Lys Lys Leu Gly Pro Cys Leu
145                 150                 155                 160
Gln Val Tyr Ala Pro Glu Val Ser Pro Glu Ser Ile Met Glu Cys Ala
                165                 170                 175
Thr Gly Lys Arg Gly Thr Gln Leu Met His Glu Asn Ala Gln Leu Thr
            180                 185                 190
Asp Ala Leu His Pro Pro His Glu Tyr Val Pro Trp Val Leu Val Asn
        195                 200                 205
Glu Lys Pro Leu Lys Asp Pro Ser Glu Leu Leu Ser Ile Val Cys Gln
    210                 215                 220
Leu Asp Gln Gly Thr Glu Lys Pro Asp Ile Cys Ser Ser Ile Ala Asp
225                 230                 235                 240
Ser Pro Arg Lys Val Cys Tyr Lys
                245
```

<210> 52
<211> 278
<212> PRT
<213> Mouse

```
<400> 52
Met Gln Thr Met Trp Gly Ser Gly Glu Leu Leu Val Ala Trp Phe Leu
 1                5                  10                  15
Val Leu Ala Ala Asp Gly Thr Thr Glu His Val Tyr Arg Pro Ser Arg
            20                  25                  30
Arg Val Cys Thr Val Gly Ile Ser Gly Gly Ser Ile Ser Glu Thr Phe
        35                  40                  45
Val Gln Arg Val Tyr Gln Pro Tyr Leu Thr Thr Cys Asp Gly His Arg
    50                  55                  60
Ala Cys Ser Thr Tyr Arg Thr Ile Tyr Arg Thr Ala Tyr Arg Arg Ser
65                  70                  75                  80
Pro Gly Val Thr Pro Ala Arg Pro Arg Tyr Ala Cys Cys Pro Gly Trp
                85                  90                  95
Lys Arg Thr Ser Gly Leu Pro Gly Ala Cys Gly Ala Ala Ile Cys Gln
            100                 105                 110
Pro Pro Cys Gly Asn Gly Gly Ser Cys Ile Arg Pro Gly His Cys Arg
        115                 120                 125
Cys Pro Val Gly Trp Gln Gly Asp Thr Cys Gln Thr Asp Val Asp Glu
    130                 135                 140
Cys Ser Thr Gly Glu Ala Ser Cys Pro Gln Arg Cys Val Asn Thr Val
145                 150                 155                 160
Gly Ser Tyr Trp Cys Gln Gly Trp Glu Gly Gln Ser Pro Ser Ala Asp
                165                 170                 175
Gly Thr Arg Cys Leu Ser Lys Glu Gly Pro Ser Pro Val Ala Pro Asn
            180                 185                 190
Pro Thr Ala Gly Val Asp Ser Met Ala Arg Glu Glu Val Tyr Arg Leu
        195                 200                 205
Gln Ala Arg Val Asp Val Leu Glu Gln Lys Leu Gln Leu Val Leu Ala
    210                 215                 220
Pro Leu His Ser Leu Ala Ser Arg Ser Thr Glu His Gly Leu Gln Asp
```

225 230 235 240
Pro Gly Ser Leu Leu Ala His Ser Phe Gln Gln Leu Asp Arg Ile Asp
245 250 255
Ser Leu Ser Glu Gln Val Ser Phe Leu Glu Glu His Leu Gly Ser Cys
260 265 270
Ser Cys Lys Lys Asp Leu
275

<210> 53
<211> 409
<212> PRT
<213> Mouse

<400> 53
Met Lys Leu Lys Gln Arg Val Val Leu Leu Ala Ile Leu Leu Val Ile
1 5 10 15
Phe Ile Phe Thr Lys Val Phe Leu Ile Asp Asn Leu Asp Thr Ser Ala
20 25 30
Ala Asn Arg Glu Asp Gln Arg Ala Phe His Arg Met Met Thr Gly Leu
35 40 45
Arg Val Glu Leu Val Pro Lys Leu Asp His Thr Leu Gln Ser Pro Trp
50 55 60
Glu Ile Ala Ala Gln Trp Val Val Pro Arg Glu Val Tyr Pro Glu Glu
65 70 75 80
Thr Pro Glu Leu Gly Ala Ile Met His Ala Met Ala Thr Lys Lys Ile
85 90 95
Ile Lys Ala Asp Val Gly Tyr Lys Gly Thr Gln Leu Lys Ala Leu Leu
100 105 110
Ile Leu Glu Gly Gly Gln Lys Val Val Phe Lys Pro Lys Arg Tyr Ser
115 120 125
Arg Asp Tyr Val Val Glu Gly Glu Pro Tyr Ala Gly Tyr Asp Arg His
130 135 140
Asn Ala Glu Val Ala Ala Phe His Leu Asp Arg Ile Leu Gly Phe Arg
145 150 155 160
Arg Ala Pro Leu Val Val Gly Arg Tyr Val Asn Leu Arg Thr Glu Val
165 170 175
Lys Pro Val Ala Thr Glu Gln Leu Leu Ser Thr Phe Leu Thr Val Gly
180 185 190
Asn Asn Thr Cys Phe Tyr Gly Lys Cys Tyr Tyr Cys Arg Glu Thr Glu
195 200 205
Pro Ala Cys Ala Asp Gly Asp Met Met Glu Gly Ser Val Thr Leu Trp
210 215 220
Leu Pro Asp Val Trp Pro Leu Gln Lys His Arg His Pro Trp Gly Arg
225 230 235 240
Thr Tyr Arg Glu Gly Lys Leu Ala Arg Trp Glu Tyr Asp Glu Ser Tyr
245 250 255
Cys Asp Ala Val Lys Lys Thr Ser Pro Tyr Asp Ser Gly Pro Arg Leu
260 265 270
Leu Asp Ile Ile Asp Thr Ala Val Phe Asp Tyr Leu Ile Gly Asn Ala
275 280 285
Asp Arg His His Tyr Glu Ser Phe Gln Asp Asp Glu Gly Ala Ser Met
290 295 300
Leu Ile Leu Leu Asp Asn Ala Lys Ser Phe Gly Asn Pro Ser Leu Asp
305 310 315 320
Glu Arg Ser Ile Leu Ala Pro Leu Tyr Gln Cys Cys Ile Ile Arg Val
325 330 335
Ser Thr Trp Asn Arg Leu Asn Tyr Leu Lys Asn Gly Val Leu Lys Ser

```
            340                 345                 350
Ala Leu Lys Ser Ala Met Ala His Asp Pro Ile Ser Pro Val Leu Ser
        355                 360                 365
Asp Pro His Leu Asp Thr Val Asp Gln Arg Leu Leu Asn Val Leu Ala
    370                 375                 380
Thr Ile Lys Gln Cys Thr Asp Gln Phe Gly Thr Asp Thr Val Leu Val
385                 390                 395                 400
Glu Asp Arg Met Pro Leu Ser His Leu
                405
```

<210> 54
<211> 697
<212> PRT
<213> Mouse

<400> 54

```
Met Arg Leu Thr Val Gly Ala Leu Leu Ala Cys Ala Ala Leu Gly Leu
 1               5                  10                  15
Cys Leu Ala Val Pro Asp Lys Thr Val Lys Trp Cys Ala Val Ser Glu
            20                  25                  30
His Glu Asn Thr Lys Cys Ile Ser Phe Arg Asp His Met Lys Thr Val
        35                  40                  45
Leu Pro Pro Asp Gly Pro Arg Leu Ala Cys Val Lys Lys Thr Ser Tyr
    50                  55                  60
Pro Asp Cys Ile Lys Ala Ile Ser Ala Ser Glu Ala Asp Ala Met Thr
65                  70                  75                  80
Leu Asp Gly Gly Trp Val Tyr Asp Ala Gly Leu Thr Pro Asn Asn Leu
                85                  90                  95
Lys Pro Val Ala Ala Glu Phe Tyr Gly Ser Val Glu His Pro Gln Thr
            100                 105                 110
Tyr Tyr Tyr Ala Val Ala Val Val Lys Lys Gly Thr Asp Phe Gln Leu
        115                 120                 125
Asn Gln Leu Glu Gly Lys Lys Ser Cys His Thr Gly Leu Gly Arg Ser
    130                 135                 140
Ala Gly Trp Val Ile Pro Ile Gly Leu Leu Phe Cys Lys Leu Ser Glu
145                 150                 155                 160
Pro Arg Ser Pro Leu Glu Lys Ala Val Ser Ser Phe Phe Ser Gly Ser
                165                 170                 175
Cys Val Pro Cys Ala Asp Pro Val Ala Phe Pro Lys Leu Cys Gln Leu
            180                 185                 190
Cys Pro Gly Cys Gly Cys Ser Ser Thr Gln Pro Phe Phe Gly Tyr Val
        195                 200                 205
Gly Ala Phe Lys Cys Leu Lys Asp Gly Gly Gly Asp Val Ala Phe Val
    210                 215                 220
Lys His Thr Thr Ile Phe Glu Val Leu Pro Glu Lys Ala Asp Arg Asp
225                 230                 235                 240
Gln Tyr Glu Leu Leu Cys Leu Asp Asn Thr Arg Lys Pro Val Asp Gln
                245                 250                 255
Tyr Glu Asp Cys Tyr Leu Ala Arg Ile Pro Ser His Ala Val Val Ala
            260                 265                 270
Arg Lys Asn Asn Gly Lys Glu Asp Leu Ile Trp Glu Ile Leu Lys Val
        275                 280                 285
Ala Gln Glu His Phe Gly Lys Gly Lys Ser Lys Asp Phe Gln Leu Phe
    290                 295                 300
Ser Ser Pro Leu Gly Lys Asp Leu Leu Phe Lys Asp Ser Ala Phe Gly
305                 310                 315                 320
Leu Leu Arg Val Pro Pro Arg Met Asp Tyr Arg Leu Tyr Leu Gly His
```

```
                325                 330                 335
Asn Tyr Val Thr Ala Ile Arg Asn Gln Gln Glu Gly Val Cys Pro Glu
            340                 345                 350
Gly Ser Ile Asp Asn Ser Pro Val Lys Trp Cys Ala Leu Ser His Leu
        355                 360                 365
Glu Arg Thr Lys Cys Asp Glu Trp Ser Ile Ile Ser Glu Gly Lys Ile
    370                 375                 380
Glu Cys Glu Ser Ala Glu Thr Thr Glu Asp Cys Ile Glu Lys Ile Val
385                 390                 395                 400
Asn Gly Glu Ala Asp Ala Met Thr Leu Asp Gly Gly His Ala Tyr Ile
                405                 410                 415
Ala Gly Gln Cys Gly Leu Val Pro Val Met Ala Glu Tyr Tyr Glu Ser
            420                 425                 430
Ser Asn Cys Ala Ile Pro Ser Gln Gln Gly Ile Phe Pro Lys Gly Tyr
        435                 440                 445
Tyr Ala Val Ala Val Val Lys Ala Ser Asp Thr Ser Ile Thr Trp Asn
    450                 455                 460
Asn Leu Lys Gly Lys Lys Ser Cys His Thr Gly Val Asp Arg Thr Ala
465                 470                 475                 480
Gly Trp Asn Ile Pro Met Gly Met Leu Tyr Asn Arg Ile Asn His Cys
                485                 490                 495
Lys Phe Asp Glu Phe Phe Ser Gln Gly Cys Ala Pro Gly Tyr Glu Lys
            500                 505                 510
Asn Ser Thr Leu Cys Asp Leu Cys Ile Gly Pro Leu Lys Cys Ala Pro
        515                 520                 525
Asn Asn Lys Glu Glu Tyr Asn Gly Tyr Thr Gly Ala Phe Arg Cys Leu
    530                 535                 540
Val Glu Lys Gly Asp Val Ala Phe Val Lys His Gln Thr Val Leu Asp
545                 550                 555                 560
Asn Thr Glu Gly Lys Asn Pro Ala Glu Trp Ala Lys Asn Leu Lys Gln
                565                 570                 575
Glu Asp Phe Glu Leu Leu Cys Pro Asp Gly Thr Arg Lys Pro Val Lys
            580                 585                 590
Asp Phe Ala Ser Cys His Leu Ala Gln Ala Pro Asn His Val Val Val
        595                 600                 605
Ser Arg Lys Glu Lys Ala Ala Arg Val Lys Ala Val Leu Thr Ser Gln
    610                 615                 620
Glu Thr Leu Phe Gly Gly Ser Asp Cys Thr Gly Asn Phe Cys Leu Phe
625                 630                 635                 640
Lys Ser Thr Thr Lys Asp Leu Leu Phe Arg Asp Asp Thr Lys Cys Phe
                645                 650                 655
Val Lys Leu Pro Glu Gly Thr Thr Pro Glu Lys Tyr Leu Gly Ala Glu
            660                 665                 670
Tyr Met Gln Ser Val Gly Asn Met Arg Lys Cys Ser Thr Ser Arg Leu
        675                 680                 685
Leu Glu Ala Cys Thr Phe His Lys His
    690                 695
```

<210> 55
<211> 400
<212> PRT
<213> Mouse

```
<400> 55
Gly Ala Pro Thr Pro Ala Tyr Val Arg Ser Ala Arg Arg Thr Glu Pro
 1               5                  10                  15
Leu Ala Ser Gly Ala Arg Ser Arg Leu Cys Gln Cys Arg Arg Val Pro
```

```
            20                  25                  30
Ala Arg Lys Gln Gly Pro Gln Glu Gln Gly Gly Ser Gly Glu Ser Thr
        35                  40                  45
Thr Ser Ser Pro Gln Trp Trp Arg Arg Trp Arg Arg Leu Trp Ser Thr
    50                  55                  60
Cys Ser Cys Ser Ala Asp Asp Arg His Thr Gly Ser His Thr Asp Leu
65                  70                  75                  80
Lys Glu Glu Thr Pro Ser Trp Thr Gln Ile Ser Val Val Phe Arg Lys
                85                  90                  95
Asp Gly Gln Asp Glu Leu Gln Ala Ala His Lys Ala His Gly Ser Gly
            100                 105                 110
Ser Pro Leu Thr Asn Gln Glu Ile Pro Ser Ser Ser Gly Ser Gly Phe
        115                 120                 125
Ile Val Ser Glu Asp Gly Leu Ile Val Thr Asn Ala His Val Leu Thr
    130                 135                 140
Asn Gln Gln Lys Ile Gln Val Glu Leu Gln Ser Gly Ala Arg Tyr Glu
145                 150                 155                 160
Ala Thr Val Lys Asp Ile Asp His Lys Leu Asp Leu Ala Leu Ile Lys
                165                 170                 175
Ile Glu Pro Asp Thr Glu Leu Pro Val Leu Leu Leu Gly Arg Ser Ser
            180                 185                 190
Asp Leu Arg Ala Gly Glu Phe Val Val Ala Leu Gly Ser Pro Phe Ser
        195                 200                 205
Leu Gln Asn Thr Val Thr Ala Gly Ile Val Ser Thr Thr Gln Arg Gly
    210                 215                 220
Gly Arg Glu Leu Gly Leu Lys Asn Ser Asp Ile Asp Tyr Ile Gln Thr
225                 230                 235                 240
Asp Ala Ile Ile Asn His Gly Asn Ser Gly Gly Pro Leu Val Asn Leu
                245                 250                 255
Asp Gly Asp Val Ile Gly Ile Asn Thr Leu Lys Val Thr Ala Gly Ile
            260                 265                 270
Ser Phe Ala Ile Pro Ser Asp Arg Ile Arg Gln Phe Leu Glu Asp Tyr
        275                 280                 285
His Glu Arg Gln Leu Lys Gly Lys Ala Pro Leu Gln Lys Lys Tyr Leu
    290                 295                 300
Gly Leu Arg Met Leu Pro Leu Thr Leu Asn Leu Leu Gln Glu Met Lys
305                 310                 315                 320
Arg Gln Asp Pro Glu Phe Pro Asp Val Ser Ser Gly Val Phe Val Tyr
                325                 330                 335
Glu Val Ile Gln Gly Ser Ala Ala Ala Ser Ser Gly Leu Arg Asp His
            340                 345                 350
Asp Val Ile Val Ser Ile Asn Gly Gln Pro Val Thr Thr Thr Thr Asp
        355                 360                 365
Val Ile Glu Ala Val Lys Asp Asn Asp Phe Leu Ser Ile Ile Val Leu
    370                 375                 380
Arg Gly Ser Gln Thr Leu Phe Leu Thr Val Thr Pro Glu Ile Ile Asn
385                 390                 395                 400
```

<210> 56
<211> 174
<212> PRT
<213> Mouse

<400> 56

```
Met Pro Ala Cys Arg Leu Cys Leu Leu Ala Ala Gly Leu Leu Leu Gly
 1               5                  10                  15
Leu Leu Leu Phe Thr Pro Ile Ser Ala Thr Gly Thr Asp Ala Glu Lys
```

```
            20                  25                  30
Pro Gly Glu Cys Pro Gln Leu Glu Pro Ile Thr Asp Cys Val Leu Glu
        35                  40                  45
Cys Thr Leu Asp Lys Asp Cys Ala Asp Asn Arg Lys Cys Cys Gln Ala
    50                  55                  60
Gly Cys Ser Ser Val Cys Ser Lys Pro Asn Gly Pro Ser Glu Gly Glu
65                  70                  75                  80
Leu Ser Gly Thr Asp Thr Lys Leu Ser Glu Thr Gly Thr Thr Thr Gln
                85                  90                  95
Ser Ala Gly Leu Asp His Thr Thr Lys Pro Pro Gly Gly Gln Val Ser
            100                 105                 110
Thr Lys Pro Pro Ala Val Thr Arg Glu Gly Leu Gly Val Arg Glu Lys
        115                 120                 125
Gln Gly Thr Cys Pro Ser Val Asp Ile Pro Lys Leu Gly Leu Cys Glu
    130                 135                 140
Asp Gln Cys Gln Val Asp Ser Gln Cys Ser Gly Asn Met Lys Cys Cys
145                 150                 155                 160
Arg Asn Gly Cys Gly Lys Met Ala Cys Thr Thr Pro Lys Phe
                165                 170
```

<210> 57
<211> 173
<212> PRT
<213> Mouse

<400> 57

```
Val Arg Asn Gly Asp Leu Phe Phe Lys Lys Val Gln Val Glu Asp Gly
 1               5                  10                  15
Gly Val Tyr Thr Cys Tyr Ala Met Gly Glu Thr Phe Asn Glu Thr Leu
            20                  25                  30
Ser Val Glu Leu Lys Val Tyr Asn Phe Thr Leu His Gly His His Asp
        35                  40                  45
Thr Leu Asn Thr Ala Tyr Thr Thr Leu Val Gly Cys Ile Leu Ser Val
    50                  55                  60
Val Leu Val Leu Ile Tyr Leu Tyr Leu Thr Pro Cys Arg Cys Trp Cys
65                  70                  75                  80
Arg Gly Val Glu Lys Pro Ser Ser His Gln Gly Asp Ser Leu Ser Ser
                85                  90                  95
Ser Met Leu Ser Thr Thr Pro Asn His Asp Pro Met Ala Gly Gly Asp
            100                 105                 110
Lys Asp Asp Gly Phe Asp Arg Arg Val Ala Phe Leu Glu Pro Ala Gly
        115                 120                 125
Pro Gly Gln Gly Gln Asn Gly Lys Leu Lys Pro Gly Asn Thr Leu Pro
    130                 135                 140
Val Pro Glu Ala Thr Gly Lys Gly Gln Arg Arg Met Ser Asp Pro Glu
145                 150                 155                 160
Ser Val Ser Ser Val Phe Ser Asp Thr Pro Ile Val Val
                165                 170
```

<210> 58
<211> 88
<212> PRT
<213> Mouse

<400> 58

```
Met Glu Glu Ile Thr Cys Ala Phe Leu Leu Leu Leu Ala Gly Leu Pro
 1               5                  10                  15
```

```
Ala Leu Glu Ala Ser Asp Pro Val Asp Lys Asp Ser Pro Phe Tyr Tyr
            20                  25                  30
Asp Trp Glu Ser Leu Gln Leu Gly Gly Leu Ile Phe Gly Gly Leu Leu
        35                  40                  45
Cys Ile Ala Gly Ile Ala Met Ala Leu Ser Gly Lys Cys Lys Cys Arg
    50                  55                  60
Arg Thr His Lys Pro Ser Ser Leu Pro Gly Lys Ala Thr Pro Leu Ile
65                  70                  75                  80
Ile Pro Gly Ser Ala Asn Thr Cys
                85
```

<210> 59
<211> 171
<212> PRT
<213> Mouse

<400> 59

```
Leu Ser Val Val Leu Gly Gly Thr Leu Tyr Ile Gly His Tyr Leu Ala
 1               5                  10                  15
Met Tyr Ser Glu Gly Ala Pro Phe Trp Thr Gly Ile Val Ala Met Leu
            20                  25                  30
Ala Gly Ala Val Ala Phe Leu His Lys Lys Arg Gly Gly Thr Cys Trp
        35                  40                  45
Ala Leu Met Arg Thr Leu Leu Val Leu Ala Ser Phe Cys Thr Ala Val
    50                  55                  60
Ala Ala Ile Val Ile Gly Ser Arg Glu Leu Asn Tyr Tyr Trp Tyr Phe
65                  70                  75                  80
Leu Gly Asp Asp Val Cys Gln Arg Asp Ser Ser Tyr Gly Trp Ser Thr
                85                  90                  95
Met Pro Arg Thr Thr Pro Val Pro Glu Glu Ala Asp Arg Ile Ala Leu
            100                 105                 110
Cys Ile Tyr Tyr Thr Ser Met Leu Lys Thr Leu Leu Met Ser Leu Gln
        115                 120                 125
Ala Met Leu Leu Gly Ile Trp Val Leu Leu Leu Leu Ala Ser Leu Thr
    130                 135                 140
Pro Val Cys Val Tyr Ile Trp Lys Arg Phe Phe Thr Lys Ala Glu Thr
145                 150                 155                 160
Glu Glu Lys Lys Leu Leu Gly Ala Ala Val Ile
                165                 170
```

<210> 60
<211> 318
<212> PRT
<213> Mouse

<400> 60

```
Met Leu Gln His Thr Ser Leu Val Leu Leu Leu Ala Ser Ile Trp Thr
 1               5                  10                  15
Thr Arg His Pro Val Gln Gly Ala Asp Leu Val Gln Asp Leu Ser Ile
            20                  25                  30
Ser Thr Cys Arg Ile Met Gly Val Ala Leu Val Gly Arg Asn Lys Asn
        35                  40                  45
Pro Gln Met Asn Phe Thr Glu Ala Asn Glu Ala Cys Lys Met Leu Gly
    50                  55                  60
Leu Thr Leu Ala Ser Arg Asp Gln Val Glu Ser Ala Gln Lys Ser Gly
65                  70                  75                  80
Phe Glu Thr Cys Ser Tyr Gly Trp Val Gly Glu Gln Phe Ser Val Ile
```

```
                85                  90                  95
Pro Arg Ile Phe Ser Asn Pro Arg Cys Gly Lys Asn Gly Lys Gly Val
            100                 105                 110
Leu Ile Trp Asn Ala Pro Ser Ser Gln Lys Phe Lys Ala Tyr Cys His
        115                 120                 125
Asn Ser Ser Asp Thr Trp Val Asn Ser Cys Ile Pro Glu Ile Val Thr
    130                 135                 140
Thr Phe Tyr Pro Val Leu Asp Thr Gln Thr Pro Ala Thr Glu Phe Ser
145                 150                 155                 160
Val Ser Ser Ser Ala Tyr Leu Ala Ser Ser Pro Asp Ser Thr Thr Pro
                165                 170                 175
Val Ser Ala Thr Thr Arg Ala Pro Pro Leu Thr Ser Met Ala Arg Lys
            180                 185                 190
Thr Lys Lys Ile Cys Ile Thr Glu Val Tyr Thr Glu Pro Ile Thr Met
        195                 200                 205
Ala Thr Glu Thr Glu Ala Phe Val Ala Ser Gly Ala Ala Phe Lys Asn
    210                 215                 220
Glu Ala Ala Gly Phe Gly Gly Val Pro Thr Ala Leu Leu Val Leu Ala
225                 230                 235                 240
Leu Leu Phe Phe Gly Ala Ala Ala Val Leu Ala Val Cys Tyr Val Lys
                245                 250                 255
Arg Tyr Val Lys Ala Phe Pro Phe Thr Thr Lys Asn Gln Gln Lys Glu
            260                 265                 270
Met Ile Glu Thr Lys Val Val Lys Glu Glu Lys Ala Asp Asp Val Asn
        275                 280                 285
Ala Asn Glu Glu Ser Lys Lys Thr Ile Lys Asn Pro Glu Glu Ala Lys
    290                 295                 300
Ser Pro Pro Lys Thr Thr Val Arg Cys Leu Glu Ala Glu Val
305                 310                 315
```

<210> 61
<211> 93
<212> PRT
<213> Mouse

<400> 61

```
Ala His Met Val Trp Ala Asn Leu Ala Val Phe Val Ile Cys Phe Leu
 1               5                  10                  15
Pro Leu His Val Val Leu Thr Val Gln Val Ser Leu Asn Leu Asn Thr
            20                  25                  30
Cys Ala Ala Arg Asp Thr Phe Ser Arg Ala Leu Ser Ile Thr Gly Lys
        35                  40                  45
Leu Ser Asp Thr Asn Cys Cys Leu Asp Ala Ile Cys Tyr Tyr Tyr Met
    50                  55                  60
Ala Arg Glu Phe Gln Glu Ala Ser Lys Pro Ala Thr Ser Ser Asn Thr
65                  70                  75                  80
Pro His Lys Ser Gln Asp Ser Gln Ile Leu Ser Leu Thr
                85                  90
```

<210> 62
<211> 408
<212> PRT
<213> Mouse

<400> 62

```
Met Ala Gln Leu Ala Arg Ala Thr Arg Ser Pro Leu Ser Trp Leu Leu
 1               5                  10                  15
```

```
Leu Leu Phe Cys Tyr Ala Leu Arg Lys Ala Gly Gly Asp Ile Arg Val
            20                  25                  30
Leu Val Pro Tyr Asn Ser Thr Gly Val Leu Gly Gly Ser Thr Thr Leu
        35                  40                  45
His Cys Ser Leu Thr Ser Asn Glu Asn Val Thr Ile Thr Gln Ile Thr
    50                  55                  60
Trp Met Lys Lys Asp Ser Gly Gly Ser His Ala Leu Val Ala Val Phe
65                  70                  75                  80
His Pro Lys Lys Gly Pro Asn Ile Lys Glu Pro Glu Arg Val Lys Phe
                85                  90                  95
Leu Ala Ala Gln Gln Asp Leu Arg Asn Ala Ser Leu Ala Ile Ser Asn
            100                 105                 110
Leu Ser Val Glu Asp Glu Gly Ile Tyr Glu Cys Gln Ile Ala Thr Phe
        115                 120                 125
Pro Arg Gly Ser Arg Ser Thr Asn Ala Trp Leu Lys Val Gln Ala Arg
    130                 135                 140
Pro Lys Asn Thr Ala Glu Ala Leu Glu Pro Ser Pro Thr Leu Ile Leu
145                 150                 155                 160
Gln Asp Val Ala Lys Cys Ile Ser Ala Asn Gly His Pro Pro Gly Arg
                165                 170                 175
Ile Ser Trp Pro Ser Asn Val Asn Gly Ser His Arg Glu Met Lys Glu
            180                 185                 190
Pro Gly Ser Gln Pro Gly Thr Thr Thr Val Thr Ser Tyr Leu Ser Met
        195                 200                 205
Val Pro Ser Arg Gln Ala Asp Gly Lys Asn Ile Thr Cys Thr Val Glu
    210                 215                 220
His Glu Ser Leu Gln Glu Leu Asp Gln Leu Leu Val Thr Leu Ser Gln
225                 230                 235                 240
Pro Tyr Pro Pro Glu Asn Val Ser Ile Ser Gly Tyr Asp Gly Asn Trp
                245                 250                 255
Tyr Val Gly Leu Thr Asn Leu Thr Leu Thr Cys Glu Ala His Ser Lys
            260                 265                 270
Pro Ala Pro Asp Met Ala Gly Tyr Asn Trp Ser Thr Asn Thr Gly Asp
        275                 280                 285
Phe Pro Asn Ser Val Lys Arg Gln Gly Asn Met Leu Leu Ile Ser Thr
    290                 295                 300
Val Glu Asp Gly Leu Asn Asn Thr Val Ile Val Cys Glu Val Thr Asn
305                 310                 315                 320
Ala Leu Gly Ser Gly Gln Gly Gln Val His Ile Ile Val Lys Glu Lys
                325                 330                 335
Pro Glu Asn Met Gln Gln Asn Thr Arg Leu His Leu Gly Tyr Ile Phe
            340                 345                 350
Leu Ile Val Phe Val Leu Ala Val Val Ile Ile Ile Ala Ala Leu Tyr
        355                 360                 365
Thr Ile Arg Arg Cys Arg His Gly Arg Ala Leu Gln Ser Asn Pro Ser
    370                 375                 380
Glu Arg Glu Asn Val Gln Tyr Ser Ser Val Asn Gly Asp Cys Arg Leu
385                 390                 395                 400
Asn Met Glu Pro Asn Ser Thr Arg
                405
```

<210> 63
<211> 278
<212> PRT
<213> Mouse

<400> 63

```
Met Phe Leu Val Gly Ser Leu Val Val Leu Cys Gly Leu Leu Ala His
 1               5                  10                  15
Ser Thr Ala Gln Leu Ala Gly Leu Pro Leu Pro Leu Gly Gln Gly Pro
            20                  25                  30
Pro Leu Pro Leu Asn Gln Gly Pro Pro Leu Pro Leu Asn Gln Gly Gln
        35                  40                  45
Leu Leu Pro Leu Ala Gln Gly Leu Pro Leu Ala Val Ser Pro Ala Leu
    50                  55                  60
Pro Ser Asn Pro Thr Asp Leu Leu Ala Gly Lys Phe Thr Asp Ala Leu
65                  70                  75                  80
Ser Gly Gly Leu Leu Ser Gly Gly Leu Leu Gly Ile Leu Glu Asn Ile
                85                  90                  95
Pro Leu Leu Asp Val Ile Lys Ser Gly Gly Gly Asn Ser Asn Gly Leu
            100                 105                 110
Val Gly Gly Leu Leu Gly Lys Leu Thr Ser Ser Val Pro Leu Leu Asn
        115                 120                 125
Asn Ile Leu Asp Ile Lys Ile Thr Asp Pro Gln Leu Leu Glu Leu Gly
    130                 135                 140
Leu Val Gln Ser Pro Asp Gly His Arg Leu Tyr Val Thr Ile Pro Leu
145                 150                 155                 160
Gly Leu Thr Leu Asn Val Asn Met Pro Val Val Gly Ser Leu Leu Gln
                165                 170                 175
Leu Ala Val Lys Leu Asn Ile Thr Ala Glu Val Leu Ala Val Lys Asp
            180                 185                 190
Asn Gln Gly Arg Ile His Leu Val Leu Gly Asp Cys Thr His Ser Pro
        195                 200                 205
Gly Ser Leu Lys Ile Ser Leu Leu Asn Gly Val Thr Pro Val Gln Ser
    210                 215                 220
Phe Leu Asp Asn Leu Thr Gly Ile Leu Thr Lys Val Leu Pro Glu Leu
225                 230                 235                 240
Ile Gln Gly Lys Val Cys Pro Leu Val Asn Gly Ile Leu Ser Gly Leu
                245                 250                 255
Asp Val Thr Leu Val His Asn Ile Ala Glu Leu Leu Ile His Gly Leu
            260                 265                 270
Gln Phe Val Ile Lys Val
        275
```

<210> 64
<211> 264
<212> PRT
<213> Mouse

<400> 64

```
Met Ala Thr Thr Thr Cys Gln Val Val Gly Leu Leu Leu Ser Leu Leu
 1               5                  10                  15
Gly Leu Ala Gly Cys Ile Ala Ala Thr Gly Met Asp Met Trp Ser Thr
            20                  25                  30
Gln Asp Leu Tyr Asp Asn Pro Val Thr Ala Val Phe Gln His Glu Gly
        35                  40                  45
Leu Trp Arg Ser Cys Val Gln Gln Ser Ser Gly Phe Thr Glu Cys Arg
    50                  55                  60
Pro Tyr Phe Thr Ile Leu Gly Leu Pro Ala Met Leu Gln Ala Val Arg
65                  70                  75                  80
Ala Leu Met Ile Val Gly Ile Val Leu Gly Val Ile Gly Ile Leu Val
                85                  90                  95
Ser Ile Phe Ala Leu Lys Cys Ile Arg Ile Gly Ser Met Asp Asp Ser
            100                 105                 110
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Ala Lys Ala Lys Met Thr Leu Thr Ser Gly Ile Leu Phe Ile Ile Ser
        115                 120                 125
Gly Ile Cys Ala Ile Ile Gly Val Ser Val Phe Ala Asn Met Leu Val
    130                 135                 140
Thr Asn Phe Trp Met Ser Thr Ala Asn Met Tyr Ser Gly Met Gly Gly
145                 150                 155                 160
Met Gly Gly Met Val Gln Thr Val Gln Thr Arg Tyr Thr Phe Gly Ala
                165                 170                 175
Ala Leu Phe Val Gly Trp Val Ala Gly Gly Leu Thr Leu Ile Gly Gly
            180                 185                 190
Val Met Met Cys Ile Ala Cys Arg Gly Leu Thr Pro Asp Asp Ser Asn
        195                 200                 205
Phe Lys Ala Val Ser Tyr His Ala Ser Gly Gln Asn Val Ala Tyr Arg
    210                 215                 220
Pro Gly Gly Phe Lys Ala Ser Thr Gly Phe Gly Ser Asn Thr Arg Asn
225                 230                 235                 240
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His Pro Thr Lys Tyr Asp Tyr Val
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<210> 65
<211> 132
<212> PRT
<213> Mouse

<400> 65

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Gly Gly Pro Arg Cys Leu Arg Val Tyr Ala Gly Leu Ile Gly Thr Val
        35                  40                  45
Val Thr Pro Asn Tyr Leu Asp Asn Val Ser Ala Arg Val Ala Pro Trp
    50                  55                  60
Cys Gly Cys Ala Ala Ser Gly Asn Arg Arg Glu Glu Cys Glu Ala Phe
65                  70                  75                  80
Arg Lys Leu Phe Thr Arg Asn Pro Cys Leu Asp Gly Ala Ile Gln Ala
                85                  90                  95
Phe Asp Ser Leu Gln Pro Ser Val Leu Gln Asp Gln Thr Ala Gly Cys
            100                 105                 110
Cys Phe Pro Arg Val Ser Trp Leu Tyr Ala Leu Thr Ala Leu Ala Leu
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<212> DNA
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<400> 66

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cgggcggcat cccccggccg ccgcacgcac aggccggcgc cctccttgcc tccctgctcc     180
ccaccgcgcc cctccggcca gcatgaggct cctggcggcc gcgctgctcc tgctgctcct     240
ggcgctgtgc gcctcgcgcg tggacgggtc caagtgtaag tgttcccgga aggggcccaa     300
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<211> 288
<212> DNA
<213> Human

<400> 67
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<211> 95
<212> PRT
<213> Human

<400> 68
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35 40 45
Glu Lys Met Val Ile Ile Thr Thr Lys Ser Val Ser Arg Tyr Arg Gly
50 55 60
Gln Glu His Cys Leu His Pro Lys Leu Gln Ser Thr Lys Arg Phe Ile
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Lys Trp Tyr Asn Ala Trp Asn Glu Lys Arg Arg Val Tyr Glu Glu
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<210> 69
<211> 234
<212> DNA
<213> Mouse

<400> 69
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atgtccaggt accggggcca ggagcactgc ctgcacccta agctgcagag caccaaacgc 180
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<210> 70
<211> 77
<212> PRT
<213> Mouse

<400> 70

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            20                  25                  30
Met Val Ile Val Thr Thr Lys Ser Met Ser Arg Tyr Arg Gly Gln Glu
        35                  40                  45
His Cys Leu His Pro Lys Leu Gln Ser Thr Lys Arg Phe Ile Lys Trp
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Tyr Asn Ala Trp Asn Glu Lys Arg Arg Val Tyr Glu Glu
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<211> 234
<212> DNA
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gtgtccaggt accgaggtca ggagcactgc ctgcacccca agctgcagag caccaagcgc 180
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<210> 72
<211> 77
<212> PRT
<213> Human

<400> 72
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            20                  25                  30
Met Val Ile Ile Thr Thr Lys Ser Val Ser Arg Tyr Arg Gly Gln Glu
        35                  40                  45
His Cys Leu His Pro Lys Leu Gln Ser Thr Lys Arg Phe Ile Lys Trp
    50                  55                  60
Tyr Asn Ala Trp Asn Glu Lys Arg Arg Val Tyr Glu Glu
65                  70                  75
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<210> 73
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<212> DNA
<213> Pinus radiata

<400> 73
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<210> 74
<211> 363
<212> DNA
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<400> 74
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cgtggagggc ggtgaactgg gtgtggctga ggccgaagag gctcgagagg cttctgagac 240
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tct 363

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00256

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl. [7]: C12N 15/11

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
SEE ELECTRONIC DATA BASES

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
SEE ELECTRONIC DATA BASES

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EMBL, GenBank, PIR , GenePept: Sequence IDs 1, 36, 2, 37, 3, 38, 4, 39, 5, 40

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GenBank Accession No. AL034558 28 July 1999 Whole Sequence w.r.t. Sequence ID 3	1 - 14
X	GenPept Accession No. CAA29045 21 March 1995 Whole Seqence Frame +2 w.r.t. Sequence ID 4	1 - 14
X	GenBank Accession No. AR018857 5 December 1998 & US 5783182 Whole Sequence w.r.t. Seqence ID 5	1 - 14

[X] Further documents are listed in the continuation of Box C [X] See patent family annex

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
28 March 2001	29.03.2001
Name and mailing address of the ISA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized officer CRAIG ALLATT Telephone No : (02) 6283 2414

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00256

C (Continuation). **DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GenPept Accession No. CAB40181 14 December 1999 Whole Seqeunce w.r.t. Sequence ID 40	1 - 14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00256

Box I **Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos :
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos :
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos :
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II **Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

See Supplemental Box

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Claims 1 - 14 partially.(See Supplemental Box)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/NZ00/00256

Supplemental Box
(To be used when the space in any of Boxes I to VIII is not sufficient)

Continuation of Box No: II

In the present application, the feature that all sequences come from "mammalian sources" does not provide a special technical feature. Genes and their expressed proteins from "mammalian sources" have been sequenced. Cells from "mammalian sources" comprise a variety of different animals and cell types. Moreover the applicant has provided no evidence that the nucleotide sequences of the present application, and the peptides they express, form a unique group of protein types. On the contrary, putative peptides derived from the nucleotide sequences of the application have functions assigned on the basis of their similarity to known proteins expressed by a variety of cell types.

The applicant has grouped the polynucleotides of the application into activity categories according to putative functions of the proteins they encode. However, most of the applicants' groupings do not form a homogenous set of proteins either in structure or function. Moreover, it is noted that most of the peptides encoded by the polynucleotides are assigned to more than one activity category.

The ISA considers that each nucleotide/peptide sequence pair (defined in Table 1 pages 8 - 19) comprises one invention and that there are 35 different inventions (the inventions being numbered sequentially).

However, as a service to the applicants, the ISA will search the first five inventions without inviting additional search fees.

Therefore the ISA has searched SEQ IDs 1, 36, 2, 37, 3, 38, 4, 39, 5, and 40.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/NZ00/00256

This Annex lists the known "A" publication level patent family members relating to the patent documents cited in the above-mentioned international search report. The Australian Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent Document Cited in Search Report		Patent Family Member					
US	5783182	AU	11609/97	CA	2237929	EP	870057
		WO	9718454				

END OF ANNEX